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Abstracts

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 17 1955

A COMPARISON OF CORTISONE AND ASPIRIN IN THE TREATMENT OF EARLY CASES OF RHEUMATOID ARTHRITIS

A SECOND REPORT BY THE JOINT COMMITTEE OF THE MEDICAL RESEARCH COUNCIL AND NUFFIELD FOUNDATION ON CLINICAL TRIALS OF CORTISONE, A.C.T.H., AND OTHER THERAPEUTIC MEASURES IN CHRONIC RHEUMATIC DISEASES*

The therapeutic trial here presented was designed to answer, as stated in the first report,† a specific but important question—namely, in early and uncomplicated cases of rheumatoid arthritis is it possible to maintain the patient's well-being more efficiently by treatment with cortisone than by treatment with aspirin? At the same time it was hoped to study the evolution of the rheumatoid process during prolonged therapy with these two different agents. In other words, the aim was to measure the therapeutic effects upon the rheumatoid process of a long-term treatment initiated while that process was still uncomplicated, either by severe anatomical changes in the joints or by metabolic disturbances resulting from a prolonged and debilitating disease.

For this purpose 61 adult patients, regarded as suitable for treatment with *either* agent, were admitted to six centres in England and Scotland. Thirty of these patients were treated with cortisone and 31 with aspirin, their allocation to one or other treatment being made entirely at random (within each centre and for patients of each sex and duration of illness). By such means two comparable groups of these early cases were constructed. Observations of the groups made one week, eight weeks, thirteen weeks, and approximately one year after the start of treatment showed that they had run a closely parallel course in nearly all respects—for example, in joint tenderness, strength of grip, tests of dexterity of hand or foot, clinical assessments of the activity of the disease and of the patient's functional capacity. "For practical purposes, therefore," the first report concluded, "there appears to have been surprisingly little to choose between cortisone and aspirin in the management of these 61 patients in the early stages of rheumatoid arthritis." In the present report the comparison is extended to approximately two years from the beginning of treatment.

Full details of the trial were given in the first report but will be briefly recapitulated here.

The Patients

Each patient included in the trial (*a*) had a polyarthritis of rheumatoid type affecting at least four joints and bilateral involvement of either hands or feet, ankles or wrists; (*b*) had had the disease for not less than three and not more than nine months; and (*c*) was aged between 17 and 59 years. A sheep-cell agglutination test was performed in most of them during the first year of observation (53 of the total 61) and gave a positive result in nearly three-quarters.

The two groups of patients, on cortisone and aspirin respectively, were initially almost identical in the numbers of men and women, in the numbers aged 17–39 and 40–59 years, and in the numbers with a duration of symptoms of three to five or six to nine months. In each of the six centres the cases admitted were almost equally divided between cortisone and aspirin. The initial equalities or inequalities in the characteristics studied will be seen in the tables that follow.

Treatment

For the first year of treatment it was laid down that therapy would be given in twelve-weeks courses separated by one week off treatment. Each course would start with a standard dosage, after which the physician was free to adjust the dose to suit the requirements of individual patients. The specified courses, given in divided doses not fewer than three times a day, were:

		Cortisone	*Aspirin*
First week:	Day 1	300 mg.	6 g.
„ „	„ 2	200 „	6 „
„ „	„ 3 to day 7 ..	100 „ daily ..	6 „ daily
Second week:	„ 8 „ „ 14 ..	50 „ „ ..	2 „ „
Third to twelfth week:	„ 15 „ „ 84 ..	Individualized at 25 to 200 mg. daily with graded withdrawal in week 12	Individualized at 1 to 8 g. daily with graded withdrawal in week 12

In the "free" period—that is, the third to twelfth week—the physician was asked to employ the minimum dosage that would restore maximal functional efficiency without producing serious side-effects. In the thirteenth week no treatment by cortisone or aspirin was given, observations and measurements being made (in this week analgesics other than aspirin could, if necessary, be given). If symptoms recurred the twelve-weeks

*The members of the Joint Committee are: Sir Henry Cohen (chairman), Dr. E. G. L. Bywaters, Dr. W. S. C. Copeman, Sir Charles Dodds, Dr. J. J. R. Duthie, Professor A. Bradford Hill, Mr. H. Osmond-Clarke, Professor F. T. G. Prunty, Dr. J. Reid, Dr. H. F. West, Professor J. H. Kellgren and Mr. W. A. Sanderson (joint secretaries).

The subcommittee and participating centres were: Professor J. H. Kellgren (chairman), Rheumatism Research Centre, Manchester; Dr. E. G. L. Bywaters, Postgraduate Medical School of London and Canadian Red Cross Memorial Hospital, Taplow; Dr. W. S. C. Copeman, West London Hospital; Dr. J. J. R. Duthie, Northern General Hospital, Edinburgh; Dr. H. F. West, Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases; Professor A. Bradford Hill; and Professor F. T. G. Prunty.

The subcommittee was assisted at these centres by the following workers, to whom it expresses its thanks: Drs. G. R. Fearnley, Margaret Fisher, J. L. Potter, Oswald Savage, J. Sharp, and M. Thompson. It is also indebted to Drs. D. E. Fletcher and K. A. Rowley for assistance in reading the *x*-ray films.

The results of the trial were analysed by Dr. J. T. Boyd, of the Statistical Research Unit of the Medical Research Council, London School of Hygiene and Tropical Medicine, and the subcommittee is greatly indebted to him for his work.

†*British Medical Journal*, 1954, **1**, 1223.

course was repeated, except that the selected dose for the individual patient replaced the standard dose of the second week.

During the second year these twelve-weeks courses were replaced by continuous treatment—unless the patient was in remission or was thought to require no maintenance dose. The dosage throughout the year was entirely at the physician's discretion, but the aim was again to employ the minimum that would produce maximum functional efficiency and relief of symptoms without producing serious side-effects.

Assessments

The clinical assessment included (*a*) a defined judgment of the patient's general functional capacity (for the five grades laid down, see Table X); (*b*) a judgment of the activity of the disease as inactive, slightly active, or very active; and (*c*) a statement whether the patient appeared to be in remission. In addition to these subjective assessments the clinician was required to measure the strength of grip for each hand. (The patient had to squeeze an oblong rubber bag 5 by 3 in. (12.5 by 7.5 cm.) inflated at a pressure of 10 mm. Hg, and the figure recorded was the average of three grips.) Two tests of dexterity were applied—namely, in patients with affected hands the time taken to tie six double knots with 12-in. (30-cm.) pieces of household string, and in patients with affected legs the time taken to go up and down ten steps. Estimates were also made of joint tenderness and of range of movement. Complications and side-effects were noted. The only obligatory laboratory tests were the blood sedimentation rate and the haemoglobin level.

Towards the end of the second year *x*-ray pictures of the hands and feet were taken and the amount of porosis and erosion revealed in each was assessed.

The Data

During the first year's observation three patients were lost from the trial—all three from the group treated with aspirin, reducing the number in that group to 28. It was concluded in the first report that two of these ought to be regarded as failures of treatment and should be remembered as such in considering the results (a male who deteriorated after some preliminary improvement, and, feeling after six months that he was gaining no benefit, was taken out of the trial and given other treatment; and a female who relapsed on leaving hospital, had a psychological breakdown, and did not attend further. The third patient, who did well on aspirin, went to New Zealand at week 30). No losses took place in the second year, and observations are available for all the 58 patients previously reported. It must be noted, however, that during the second year six patients (one on cortisone and five on aspirin) were known to have received some treatment other than that laid down (there was, however, no transfer from one treatment group to the other). These were:

(*a*) Two patients on aspirin who did not attend regularly in the second year (Postgraduate Medical School Centre).

(*b*) Two patients on aspirin (West London Centre) who had their aspirin therapy discontinued in weeks 55 and 72.

(*c*) One patient on aspirin (Edinburgh Centre) who had severe side-effects and the drug discontinued in week 55.

(*d*) One patient on cortisone (Edinburgh Centre) who had severe side-effects and the hormone discontinued in week 55.

These patients have been retained in their original groups, which are thus composed of 30 patients on cortisone, one of whom was given some other treatment (not aspirin), and 28 patients on aspirin, five of whom were given some other treatment (not hormone).

The treatment schedule laid down for the second year required continuous therapy until the last four weeks (except in cases already in remission or thought not to require any maintenance dose). In weeks 100 to 104 a gradual "tapering off" was called for, followed by four weeks without treatment and an assessment at the end of this period—that is, in week 108. The centres were not, however, able to fulfil this schedule in all cases, and for about one-third of each group no "off-treatment" assessment was made (nine of each treatment group). In some cases the withdrawal of treatment was regarded as unjustifiable, and in others signs of relapse following a reduction of dosage caused the full amount required for maintenance to be restored. On the other hand, assessments were available for all 58 patients at some point close to the end of the year while they were still on their personal dosage. The week chosen for analysis, therefore, was, for each patient, that week of personal dosage which provided assessments and was nearest to week 104—with the proviso that it must lie at least four weeks before an off-treatment week—that is, before any "tapering off", of dosage would have begun. There were six patients (three on cortisone and three on aspirin) who had been off treatment for all or part of the second year; in these cases the personal dosage was taken to be nil and the week nearest to the end of the year was chosen for analysis. The actual points taken lay between the 96th and 112th weeks in all cases.

Results

In the first report the changes under treatment were shown for each group between the start of treatment and the end of the first week, between week 1 and week 8, and between week 8 and one year. It has not been thought necessary to present the intermediate data again, and the tables that follow show the picture at the start of treatment and the end of the first and second years.

(a) Joint Tenderness

In reaching the figures for joint tenderness set out in Table I an overall "tenderness" index was first computed separately for each patient by taking the average of his recorded joints. The mean of these averages gave, at each point of time, an index for the treatment group as a whole. It will be seen that the average position at the start of treatment was almost identical in the two groups—namely,

TABLE I.—*The Average Levels of the Joint Tenderness Index**

Joints Measured	Treatment Group	Average Joint Tenderness		
		Start of Treatment	End of 1 Year	End of 2 Years
All relevant joints (including wrist and hand, given below)	Cortisone	1·91	0·74	0·72
	Aspirin	1·89	0·76	0·58
Wrist-joints	Cortisone	1·80	1·00	0·93
	Aspirin	1·93	0·96	0·73
Small joints of hand ..	Cortisone	2·25	0·58	0·63
	Aspirin	2·05	0·53	0·31

* Tenderness was graded on the scale 0 for no pain, 1 for slight pain, 2 for wincing, and 3 for wincing and withdrawal. The records have been used as an ordinary numerical scale.

TABLE II.—*Joint Tenderness Index (all relevant joints) at the End of Two Years Related to the Initial Levels of Tenderness. Number of Patients*

Joint Tenderness at Start of Treatment	Treatment Group and No. of Patients	Joint Tenderness at End of 2 Years				
		0	Under 1	1–	2–	3
Under 1 ..	Cortisone .. 1		1			
	Aspirin .. 3	1	2			
1– ..	Cortisone .. 13	2	6	4	1	
	Aspirin .. 7	4	3			
2– ..	Cortisone .. 11	3	4	3	1	
	Aspirin .. 13	3	5	4	1	
3 ..	Cortisone .. 5	2	2	1		
	Aspirin .. 5	1	3			1
Total ..	Cortisone .. 30	7	13	8	2	0
	Aspirin .. 28	9	13	4	1	1

1.91 cortisone and 1.89 aspirin—and that the decline in tenderness during the first year was considerable and strikingly similar—to 0.74 cortisone and 0.76 aspirin. During the second year the average for the cortisone group has remained almost the same (0.72), while for the aspirin group the figure has declined further to 0.58. Division of the joints into those of the wrists and of the hand (the main components of the total index) gives a very similar picture in each group—that is, equality at one year and a lower figure in the aspirin group at two years. The differences at two years are not, however, statistically significant, and too much emphasis must not be placed upon them. Table II gives the numbers of patients with different levels of joint tenderness at the start of treatment and at the end of two years. The equality of the two groups is again noticeable. Thus, for the joints recorded at the start of treatment, 7 of the 30 patients on cortisone had no remaining joint tenderness at all at the end of two years, in 13 it was slight, and in 10 it was more definite. The corresponding figures for the 28 observed patients on aspirin were 9, 13, and 6. The numbers available are small, but the same equality of trend is suggested in each subdivision of the table.

(b) Range of Movement and Strength of Grip

Table III gives the figures for range of movement in the wrists and strength of grip. In these respects the cortisone group had, by chance and on the average, some advantage over the aspirin group when treatment was started. At the end of one year both groups had improved considerably. At this point of time the averages of the cortisone group remained above those of the aspirin group, but the advantage was no greater than had been observed at the start of treatment. At the end of two years even that gap has narrowed, both groups having shown a very slight deterioration during the second year and there being no significant difference between them at the end of the second year. The frequency with which various ranges of wrist movement were observed are shown in Table IV, and the changes in strength of grip in Table V. Neither table reveals any clear advantage to one or other treatment.

TABLE III.—*The Average Measurements of (a) Range of Wrist Movement and (b) Strength of Grip*

Characteristic Measured	Treatment Group	Average Measurement		
		Start of Treatment	End of 1 Year	End of 2 Years
Range of wrist movement (in degrees)	Cortisone	99*	120*	111
	Aspirin	78	103	103
Strength of grip (in mm. Hg) left hand	Cortisone	138	202*	187
	Aspirin	111	164	158
Strength of grip (in mm. Hg) right hand	Cortisone	134	187	186
	Aspirin	116	166	164

* The mean of the cortisone group was significantly greater than the mean of the aspirin group.

TABLE IV.—*Range of Movement (wrists) at Two Years Related to the Initial Range of Movement. Number of Wrists Involved*

Range of Movement (Degrees) at Start of Treatment	Treatment Group	Range of Movement at End of 2 Years (Degrees)			
		0–	50–	100–	150+
0–	2 Cortisone		2		
	9 Aspirin		5	3	1
50–	12 Cortisone	1	5	5	1
	13 Aspirin		6	6	1
100–	12 Cortisone		2	6	4
	11 Aspirin		6	4	1
150+	3 Cortisone			1	2
	0 Aspirin				
Total	29 Cortisone	1	9	12	7
	33 Aspirin	0	17	13	3

TABLE V.—*Number of Patients Showing Given Improvement or Deterioration in Their Strength of Grip (in mm. Hg) Between Start of Treatment and End of Two Years*

Treatment Group and No. of Patients	Improved by 100 mm. or More	Improved by up to 100 mm.	No Change	Deteriorated by up to 100 mm.	Deteriorated by 100 mm. or More
Left hand:					
30 Cortisone	7	14	1	6	2
28 Aspirin	4	15	3	6	—
Right hand:					
30 Cortisone	11	12	1	5	1
28 Aspirin	7	14	1	6	—

(c) Tests of Dexterity

Table VI gives the results of the timing tests. The improvement noted at the end of one year has been maintained, but not increased, during the second year of treatment. The two treatment groups remain very similar in these respects.

TABLE VI.—*The Average Time Taken to (a) Tie Six Knots and (b) Go Up and Down Ten Steps by Patients with Affected Hands and Legs Respectively*

Characteristic Measured	Treatment Group	Average Time (in Seconds)		
		Start of Treatment	End of 1 Year	End of 2 Years*
Time to tie 6 knots	Cortisone	38	29	29
	Aspirin	41	34	33
Time to go up and down 10 steps	Cortisone	14	11	11
	Aspirin	18	13	11

* 8 patients (5 cortisone, 3 aspirin) included in the earlier averages had no recording for either dexterity test at two years.

(d) Haemoglobin Level and Blood Sedimentation Rate

During the first year of the trial it was found that the haemoglobin level and blood sedimentation rate responded, on the average, rather more favourably to cortisone than to aspirin. During the second year this advantage to the cortisone group has not been maintained (Table VII). While its average values for the haemoglobin level and erythrocyte sedimentation rates have both remained practically unchanged, the average haemoglobin value in the aspirin group has risen and the average E.S.R. has fallen. As a result the two treatment groups differ little in the average haemoglobin level and negligibly in the average E.S.R. at the end of two years. Looking beneath the averages to individual levels of the E.S.R., the same picture of close similarity is revealed (Table VIII). Taking under 20 mm./hour as the level of normality, 10 of the 30 patients on cortisone and 11 of the 28 on aspirin had a normal E.S.R. at the end of two years of treatment, while 11 and

TABLE VII.—*The Average Levels of (a) Haemoglobin and (b) Blood Sedimentation Rate*

Characteristic Measured	Treatment Group	Average Measurement		
		Start of Treatment	End of 1 Year	End of 2 Years
Haemoglobin (g.%)	Cortisone	12·2	13·1*	13·0
	Aspirin	12·1	11·3	12·3
E.S.R. (mm./hr.)	Cortisone	42	27	29
	Aspirin	42	35	28

* The averages shown by the cortisone and aspirin groups differ significantly.

TABLE VIII.—*Number of Patients With Given Blood Sedimentation Rates at the End of Two Years Related to Their Rates at the Start of Treatment*

E.S.R. (mm./hr.) at Start of Treatment	Treatment Group and No. of Patients	E.S.R. (mm./hr.) at End of 2 Years			
		0–	20–	40–	60+
0–	9 Cortisone	6	3		
	5 Aspirin	3	2		
20–	6 Cortisone	1	3	2	
	11 Aspirin	5	4	2	
40–	9 Cortisone	2	5	1	1
	7 Aspirin	2	5		
60+	6 Cortisone	1		3	2
	5 Aspirin	1	1	2	1
Total ..	30 Cortisone	10	11	6	3
	28 Aspirin	11	12	4	1

12 respectively had an elevated rate (20–39) and nine and five had a considerably elevated rate (40 or over). Within the subgroups with different levels at the start of treatment the trend also appears to have been remarkably similar in the two groups.

(e) Clinical Assessments

At the end of the second year four patients on cortisone and four on aspirin were reported to be in remission. The overall clinical assessments of condition at the end of the first and second years are shown in Table IX.

TABLE IX.—*Clinical Assessment of Activity at End of One Year and End of Two Years*

Grade	End of 1 Year		End of 2 Years	
	Cortisone	Aspirin	Cortisone	Aspirin
Inactive ..	2	2	4	4
Slightly active ..	21	19	20	19
Very active ..	7	7	6	5
Total ..	30	28	30	28

The assessments of functional capacity are given in Table X, and at the end of two years the two treatment groups still remain, as was noted at one year, more remarkable for their similarity than for their dissimilarity. In each treatment group 21 patients were regarded as capable either of full work (grade 1) or of light work (grade 2), and subdivision of them shows 14 patients in grade 1 in the cortisone group and 13 in the aspirin group. Seven of the 30 patients on cortisone remained seriously incapacitated (grade 3), compared with 5 of the 26 patients on aspirin. Only two patients, both on cortisone, were still grossly incapacitated, and against this may be placed the two aspirin cases who progressed unfavourably in the first year and were lost sight of—that is, putting the most unfavourable complexion upon them.

TABLE X.—*Number of Patients with Given Functional Capacity at Different Stages of the Trial**

Treatment Group	Time of Assessment	Functional Capacity			Total
		1 or 2	3	4 or 5	
Cortisone	Start of treatment	4	18	8	30
Aspirin		5	18	6	29†
Cortisone	End of 1 year	23	5	2	30
Aspirin		21	5	0	26
Cortisone	End of 2 years	21	7	2	30
Aspirin		21	5	0	26

* Functional capacity grades were:
Grade 1: Fully employed or employable in usual work and able to undertake normal physical recreation.
„ 2: Doing light or part-time work and only limited physical recreation. For housewives, all except the heaviest housework.
„ 3: Not employed and unemployable. No physical recreations. Housewives only light housework and limited shopping.
„ 4: Confined to house or wheel-chair, but able to look after themselves in essentials of life. Hospital patients confined to bed.
„ 5: Completely bedridden.

† No record was made in this respect for two patients, and three were lost sight of during the first year of the trial. The two patients not assessed at the start of treatment had functional capacities at the end of two years of 1 and 2 respectively.

(f) X-ray Observations

X-ray films of the hands were taken for all 30 patients on cortisone and for 27 of the 28 patients on aspirin during the second half of the second year of the trial. For the feet, films were available for 26 patients on cortisone and 24 on aspirin. All these films were read independently by three observers (a clinician at one of the centres and two radiologists), who assessed the degree of porosis and erosion present in each case without knowing the treatment group to which it belonged. The results are shown in Tables XI and XII. It is clear that while observers B and C were similar in their interpretations of the films, observer A had a quite different standard—particularly in porosis. For instance, no or doubtful porosis of the hands (grades 0 and 1) was recorded for 20 and 21 patients on cortisone by observers B and C, but for only 14 by observer A. An

TABLE XI.—*X-ray Films of the Hand. Number of Patients with Given Gradings at the End of Two Years by Three Independent Observers*

Grade*	Cortisone			Aspirin		
	Observer			Observer		
	A	B	C	A	B	C
	Porosis					
0	5	16	13	4	10	7
1	9	4	8	6	4	11
2	8	7	7	11	10	8
3	5	2	1	4	3	1
4	3	1	1	2	0	0
Total ..	30	30	30	27	27	27
Average grade	1·73	0·93	0·97	1·78	1·22	1·11
	Erosion					
0	6	7	9	3	5	3
1	5	7	5	3	4	4
2	11	12	12	8	7	16
3	5	3	4	11	10	4
4	3	1	0	2	1	0
Total ..	30	30	30	27	27	27
Average grade	1·80	1·47	1·37	2·22	1·93	1·78

* Gradings of porosis and erosion were: 0 = Nil. 1 = Doubtful. 2 = Slight. 3 = Moderate. 4 = Severe.

TABLE XII.—*X-ray Films of the Feet. Number of Patients with Given Gradings at the End of Two Years by Three Independent Observers*

Grade	Cortisone			Aspirin		
	Observer			Observer		
	A	B	C	A	B	C
	Porosis					
0	5	18	14	3	14	12
1	8	3	9	6	6	8
2	5	3	1	10	3	2
3	6	1	2	4	1	2
4	2	1	0	1	0	0
Total ..	26	26	26	24	24	24
Average grade	1·69	0·62	0·65	1·75	0·63	0·75
	Erosion					
0	9	7	7	5	6	3
1	4	10	9	0	3	6
2	7	4	9	10	7	12
3	4	4	1	5	8	3
4	2	1	0	4	0	0
Total ..	26	26	26	24	24	24
Average grade	1·46	1·31	1·15	2·13	1·71	1·63

analysis of variance shows these differences between the observers, in their gradings of both porosis and erosion, to be highly significant ($P<0.001$).

Comparison between the treatment groups shows that for each observer the mean figures for porosis and erosion of the hands and feet are rather higher in the aspirin group than in the cortisone group. The differences are very small for porosis but more marked for erosion. The analysis of variance shows that they are not statistically significant. A simple summation of the readings of the three observers gives the following proportions with some degree of porosis or erosion (grades 2, 3, and 4):

	Porosis		*Erosion*	
	Cortisone	*Aspirin*	*Cortisone*	*Aspirin*
Hands ..	39%	48%	57%	73%
Feet ..	27%	32%	41%	68%

The differences are again relatively slight (except, perhaps, for erosion of the feet), and, with the numbers of patients involved, none of them is significant. It is not possible to compare the *changes* that have taken place in these respects in the two treatment groups, since *x*-ray films were not one of the requirements at the start of the trial. *X*-ray films were, however, taken initially in some patients, and it is possible to make use of these. Thus there were 16 patients in the aspirin group and 25 in the cortisone group for whom *x*-ray films of the hands were available at the start of treatment and at the end of two years, and 8 and 11

respectively with *x*-ray films of the feet. The latter are too few to be of any value, and examination suggests also that they may well be an unrepresentative group. On the other hand, the 16 patients on aspirin for whom *x*-ray pictures of the hands were available had at the start of treatment average measurements in joint tenderness, grip, etc., very similar to the total aspirin group. In these respects, therefore, those whose hands were *x*-rayed do not appear to be a biased group. To allow comparison of the recorded changes in porosis and erosion in these 16 patients on aspirin each has been matched with a cortisone patient with the same initial degree of porosis or erosion. (Where more than one appropriate cortisone patient was available a random choice was made.) This comparison of the 16 matched patients shows that at entry to the trial some degree of porosis (slight, moderate, or severe) was recorded as present in 45% of the readings in each treatment group. At the end of two years the percentage was 40 in the cortisone group and 55 in the aspirin group, slight and not significant changes. In erosion the initial percentage was only 6 in each treatment group, but at the end of two years this had increased to 65 in the cortisone group and 74 in the aspirin group. The change here is large, but is similar in both groups. On the basis of these admittedly limited figures for the hands there is clearly no material difference between the progression of the two treatment groups.

(g) Side-effects

During the first year of treatment side-effects were recorded for 19 patients in the cortisone group and 21 in the aspirin group. During the second year the numbers were 19 and 12. Most of these patients had more than one side-effect, the most frequent in the cortisone group being oedema of the ankles (8 cases), moon-face or rubicundity (6), depression (5), euphoria (4), and obesity (3); in the aspirin group the most frequent were nausea, dyspepsia, or anorexia (6), tinnitus (4), and oedema of the ankles (3). In only two cases, one in each treatment group, were these side-effects severe enough to necessitate the discontinuance of treatment. The patient on cortisone, a woman aged 36, suffered from persistent and severe headache, depression, dyspepsia, and vomiting, and had occasional casts of red blood cells in the urine. The patient on aspirin, a man aged 40, had marked dyspepsia and vomiting.

The Maintenance Doses

The maintenance doses that were being employed at the end of the second year are set out in Table XIII. They do not differ appreciably from those in use at the end of the first year, when the average values were 80 mg. of cortisone and 4.5 g. of aspirin.

TABLE XIII.—*Daily Maintenance Doses Being Administered at the End of the Second Year (Before any Tapering Off)*

Cortisone (mg./day)	No. of Patients on Given Dose	Aspirin (g./day)	No. of Patients on Given Dose
125	1	6·7	2
100	6	6	2
75	11		
62½	3	5*	4
50	3	4	9
37½	1	3·3	1
25	1	2·7	1
		2	1
Total	26	Total	20
Mean value	75 mg.	Mean value	4·5 g.
Not receiving cortisone	4	Not receiving aspirin	8

* Including 1 at 5·3.

Discussion

In the first year of this trial of the treatment of early cases of rheumatoid arthritis it was decided that the treatment should be tapered off at the end of each three-months period and then withheld for a week to allow an assessment of the patient's condition. At the end of the first of these courses of treatment it was found that there was distinct "relapse" in some of the patients, though, it is important to note, an equal degree of "relapse" occurred on the two forms of treatment, cortisone and aspirin. Such "relapses," even though minor in degree, were clearly undesirable, and it was therefore decided that treatment should be continuous throughout the second year of the trial (and, indeed, in a number of cases it became continuous before the end of the first year). At the end of this continuous treatment, which allowed a maintenance dose entirely at the physician's discretion, an assessment was made, usually while the patient was on a maintenance dose (or on no dose if in remission). Thus comparisons can now be made between the two groups at approximately the end of two years of treatment (between weeks 96 and 112 from the start of treatment), the second year's treatment having been uninterrupted.

In total, 61 patients were admitted to the trial, 30 being allocated at random to cortisone and 31 to aspirin. Three of the patients in the aspirin group were lost sight of during the first year, of whom two could be regarded as failures of that treatment and one, who migrated, as a success so far as it went. During the second year none has been lost to sight, and measurements and assessments are available for all 58 patients in most respects. On the other hand, it must be noted that the aspirin group contains four patients who had some additional therapy (not hormone) during the second year, while there was also one patient in the aspirin group and one in the cortisone group whose treatment was discontinued as a result of severe side-effects. These few changes are hardly sufficient to disturb materially the comparison of the two groups. It may be added, too, that a separate analysis has been made, for several of the features given in the tables above, for the patients on cortisone and aspirin who were at the three centres where the only changes were the discontinuance of treatment in one cortisone and one aspirin case. Here there could be no bias, and the results were found to parallel closely those set out in full for the total groups. Attention may therefore be confined to these total groups.

The results of the trial continue at the end of two years to show a similarity between the two treatment groups that is almost remarkable. In some respects the average values for the two groups have come even closer together than they were at the end of one year—either by slight improvement in the aspirin group or by a slight falling-off in the cortisone group. This applies to the range of wrist movement, the strength of grip, and the tests of dexterity. In joint tenderness the cortisone group shows no change in its average index, while the aspirin group shows a reduction. None of these differences, however, is statistically significant. At the end of one year, on the other hand, it was shown that the haemoglobin level and blood sedimentation rate had, on the average, responded rather more favourably to cortisone than to aspirin. This advantage of the cortisone group has vanished during the second year. The mean and frequency distribution of the sedimentation rates are almost identical and the mean haemoglobin levels no longer differ significantly.

A new measure has been introduced to the trial by means of *x*-ray films of the hands and feet of the patients, assessed independently and "blindly" by three observers. Their estimates of the degree of porosis and erosion shown by each patient reveal very little difference between the two treatment groups in respect of porosis, but some excess of erosion in the aspirin group. This excess, however, is not more than might fairly easily arise by chance. The relative position of the two groups in this respect at the start of treatment is unknown, since *x*-ray examinations were not demanded at entry. A study of such *x*-ray films of the hands as were available suggests, however, that neither group has changed appreciably in the incidence of porosis. Both groups show a very considerable rise in the recorded incidence of erosion, but differ little from one another.

Clinical assessments of the patient's condition continue to show no difference between the two groups. With almost

equal numbers at risk, four in each group were in remission, six on cortisone and five on aspirin were "very active," 14 on cortisone and 13 on aspirin were regarded as capable of doing their usual work and of taking normal physical recreation, nine on cortisone were still gravely incapacitated and seven on aspirin (including here the two unsuccessful cases lost to sight in the first year). As at the end of one year the two groups retain their equality.

Summary

A further report is made on 61 patients who were allocated at random to treatment with either cortisone (30 cases) or aspirin (31 cases) while they were still in the early stages of rheumatoid arthritis. In their second year of therapy treatment with one or other agent has been continuous, and "individualized" by the physician in charge of the patient to meet each patient's needs. At approximately the end of two years of treatment 58 of the original 61 patients have been reassessed clinically, submitted to some simple objective tests, had *x*-ray films taken of their hands and feet, and had their haemoglobin levels and blood sedimentation rates measured. In no respect do the two groups differ by more than might easily be due to chance, and in most respects they are distinguished more by their equalities than by their differences. At the end of two years, therefore, as previously reported at the end of one year, it appears that for practical purposes there has been remarkably little to choose between cortisone and aspirin in the management of this group of patients.

INTRAMUSCULAR IRON IN INFANCY

BY

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A good doctor will always be chary of using, or recommending, parenteral therapy when oral treatment can lead to equally good results less unpleasantly. Iron has been given by mouth for many years with excellent results, both in the ferric state as iron and ammonium citrate, and more recently as ferrous sulphate, which has been used increasingly since it has been recognized that only in the ferrous state can iron be absorbed and that ferric salts have to be reduced by the acid gastric juice before they can be utilized. Naturally, iron has been used particularly in paediatrics for the treatment of iron-deficiency anaemia—that is, of nutritional origin—and in infants so affected the associated hypochlorhydria can only act as a deterrent to full utilization of ferric salts. In any case, it is well known that only a portion, even of the ferrous salts, is absorbed when given by mouth, and the size of this portion depends on the physiological functioning of the gastro-intestinal secretory and absorptive mechanisms. With ferrous sulphate it is usually considered that not more than 14% utilization can be obtained. A utilization coefficient of 28% is given for ferrous gluconate (Haler, 1952). Although oral iron is usually effective, it has certain disadvantages. It is unpleasant, and may cause vomiting and intestinal upsets. In some cases the parents do not give the prescribed dose, or give it only irregularly, and if it causes any upset they stop further treatment without informing the doctor, and so the desired effect is not achieved. It is probable that the intestinal mucosal barrier prevents the absorption of iron in excess of immediate haemoglobin requirements, so that adequate stores are never accumulated. In addition, it takes some time for the effects of oral iron to be evident clinically, and this time factor is of great importance. Often infants with nutritional anaemia are not seen until the anaemia is well developed, and, as anaemia probably represents a final stage of a general tissue depletion, an affected infant will have been disturbed metabolically for some time previously. He may have been unwell generally, and, when exposed to the hazards of infection, reacted less well than a normal infant. Any increased speed of response to treatment would therefore be most valuable.

Intravenous iron preparations are utilized completely and rapidly. But, as is to be expected from the difficulty of the administration of these substances, they are not often used in practice. Several observers have reported their experiences with small groups of children (Granrud and Øster, 1950; Hanna and Shehata, 1951; Beaujon, 1951; Hagberg, 1951; Schöner, 1952; Stransky and Dauis-Lawas, 1952; Wiesener, 1952). The largest series was that of Dickstein and his colleagues (1952), who treated 80 infants and children, of whom 66 were suffering from nutritional anaemia.

The introduction of an active, efficient, relatively painless intramuscular preparation, free from undesirable side-effects, would be a welcome advance in therapy for infants unable to tolerate or utilize oral iron and for those in whom rapidity of response was important, or in those in whom transfusion was difficult technically and iron might be a fair substitute.

There is, of course, already a British Pharmacopoeial preparation of iron for injection. It is, however, very painful and requires the addition of a local analgesic with every injection.

Present Investigation

This report describes the use of a new product—"imferon"—which is a stable, non-irritant preparation of an iron-dextran complex, containing 50 mg. of elemental iron per ml. Treatment of adults with this preparation has already been described (Baird and Podmore, 1954; Cappell *et al.*, 1954; Scott and Govan, 1954; Jennison and Ellis, 1954), but there have not so far been any reports of its use in infants.

We have treated more than 100 infants and children with this preparation, but we are here reporting only the results with initial groups who have been followed up for some months. The first infants treated were suffering from nutritional anaemia. Included among these were a few infants who had been premature at birth and who presented at 10–12 months of age with the "anaemia of prematurity." They responded so well to treatment that we next treated a group of infants attending the follow-up clinic for premature infants, many of them irregular attenders who, on being rounded up, were found to be anaemic. We then decided to try the effect of the prophylactic use of intramuscular iron in premature infants in the hope of preventing the otherwise almost inevitable anaemia of prematurity from developing later. In addition, there were several other infants who were anaemic as a result of haemorrhage, and these we have grouped as surgical cases.

Results

All haemoglobin values are on the scale 100% = 14.8 g. Sideroblasts were looked for in methanol-fixed films and

stained with equal parts of 5% HCl and 5% potassium ferrocyanide for 10 minutes at 56° C. in Coplin jars.

Nutritional Anaemia

There were 21 infants in this initial group (Table I). All were in-patients who had been admitted for various reasons—for example, failure to thrive, pallor, splenomegaly, bronchitis—and in whom examination of their peripheral blood showed anaemia with a low colour index. Marrow specimens were taken from the iliac crests of these infants before treatment was begun and showed the typical features of a nutritional iron-deficiency anaemia. Sideroblasts were looked for but rarely seen, and did not exceed 2% in any marrow. The amount of imferon injected at any one time was usually 50 mg. (1 ml.), and the total dose varied from 150 to 500 mg. The average number of injections was five. There was obvious rapid clinical improvement in all cases, as shown by the return of appetite, change of disposition, improvement in colour, and gain in weight. The average haemoglobin level before treatment was 54.5%; after two weeks this had risen to 75.1%, and at ten weeks or more was 87%. This improvement has been maintained, and some of the infants seen many months later still have normal blood pictures. The daily rise in haemoglobin during the first two weeks after treatment was almost 1.5%.

TABLE I.—*Nutritional Anaemia*

Case No.	Age (Months)	Dose (mg.)	Haemoglobin %						
			Initial	Weeks					
				1	2	4	6	8	10+
1	24	250	50	64	—	—	—	—	86
2	9	150	66	82	—	—	86	—	80
3	6	225	48	—	68	—	—	86	94
4	4	300	46	—	82	—	—	—	88
5	19	200	56	—	82	—	—	80	94
6	14	250	50	—	80	—	—	—	98
7	21	225	56	—	—	—	—	—	94
8	19	250	58	—	80	—	—	92	86
9	13	300	52	—	78	—	74	—	80
10	7	400	58	82	—	84	—	88	90
11	12	250	52	—	62	80	—	—	—
12	10	300	38	—	80	—	—	—	—
13	2	175	60	—	—	80	—	—	86
14	18	300	68	—	—	—	—	—	80
15	24	500	46	—	—	68	76	—	—
16	14	200	70	—	—	85	—	—	—
17	19	250	64	—	80	—	—	—	80
18	20	150	58	66	72	—	—	—	—
19	10	150	48	60	80	—	—	—	—
20	3	150	68	—	76	—	—	—	82
21	27	400	30	38	56	76	—	80	86
Average	14·5	256	54·5	65·3	75·1	78·8	78·7	83·2	87

Some of the infants underwent marrow examination after treatment, and sideroblasts were seen in all of these, the number varying from 6% to 46% of the total nucleated red cells. The distribution of the haemoglobin levels before and after treatment is shown in Fig. 1. A typical case in this series is illustrated in Fig. 2. This patient was a boy of 2 years and 3 months who was admitted with marked pallor and hepatomegaly. He had developed normally since birth, but had never eaten any form of meat or fish. Rapid improvement followed the injection of 400 mg. of imferon in four doses on alternate days.

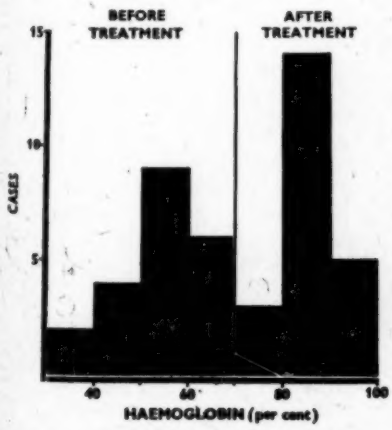

FIG. 1.—Nutritional anaemia. Haemoglobin levels before and after treatment.

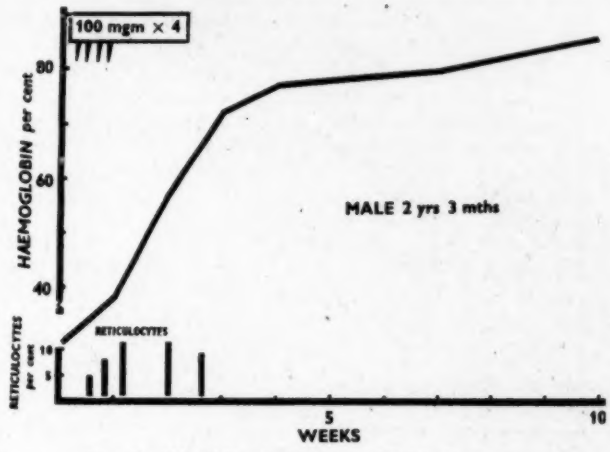

FIG. 2.—Nutritional anaemia. Illustrative case.

Anaemia of Prematurity—Treatment

The 14 babies in this group are shown in Table II. Most of these cases were infants whose mothers had failed to bring them regularly to the premature baby clinic and were found to be anaemic when they eventually attended. A few had had oral iron prescribed but for various reasons had not responded. Marrow examinations were not carried out in this group. Again the usual dose was 50 mg. (1 ml.), but some received an injection of 100 mg. (2 ml.)—1 ml. into each buttock. The total dose varied from 100 to 400 mg. The average haemoglobin before treatment was 49.3%, which rapidly increased to 69.6% at two weeks and was 77.5% when the infants were seen at ten weeks or later. The average daily rise in haemoglobin was more than 1.4%. Fig. 3 shows the distribution of the haemoglobin levels before and after treatment, and Fig. 4 shows the response of a typical case.

TABLE II.—*Anaemia of Prematurity—Therapy*

Case No.	Age (Months)	Dose (mg.)	Haemoglobin %						
			Initial	Weeks					
				1	2	4	6	8	10
1	15	400	50	64	64	68	—	—	—
2	14	300	56	64	70	80	—	—	82
3	11	150	54	68	—	—	—	—	74
4	10	300	40	58	70	76	—	—	—
5	10	300	50	62	72	76	74	—	78
6	7	300	48	66	72	76	—	78	80
7	7	200	48	—	—	66	—	78	—
8	7	150	52	66	74	—	—	—	—
9	6	200	58	—	—	80	80	—	82
10	6	150	52	—	64	78	—	78	82
11	5	150	50	62	74	72	—	—	—
12	5	150	48	50	68	76	—	—	66*
13	4	100	46	58	62	66	68	—	76
14	2	150	40	58	76	—	—	78	—
Average	8	214	49·3	61·4	69·6	74	74	78	77·5

* This infant had bronchitis at the eighth week.

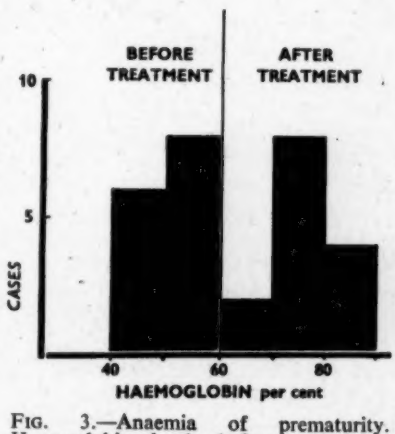

FIG. 3.—Anaemia of prematurity. Haemoglobin levels before and after treatment.

Since this new preparation was first tried, more than a year ago, our figures for these two groups have more than doubled and the results remain consistently good.

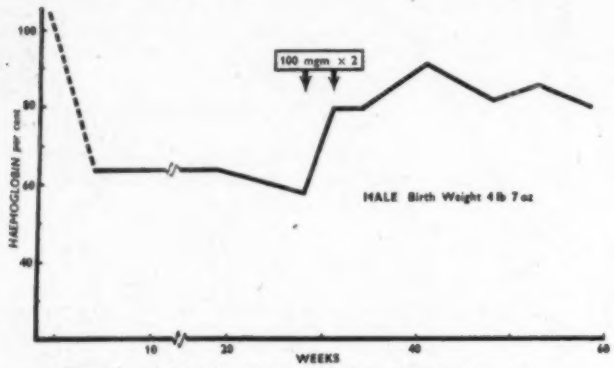

FIG. 4.—Anaemia of prematurity. Illustrative case.

Anaemia of Prematurity—Prophylaxis

Two groups of 10 premature babies were used. Alternate admissions to the premature baby unit were given injections during the third week after birth and the others were observed as controls. The treated babies with birth weights of less than 4 lb. (1.8 kg.) were given 250 mg. and those between 4 and 5 lb. (1.8 and 2.3 kg.) 150 mg. in 50-mg. (1-ml.) doses. The doses were based on the rapid increase in weight that was to be expected during the first six months of life. The results are shown in Table III and in Fig. 5. Although parenteral iron does not prevent the fall in haemoglobin during the first few weeks of life any more than does oral iron, a significant difference in favour of the treated group has appeared by the 16th week and persists.

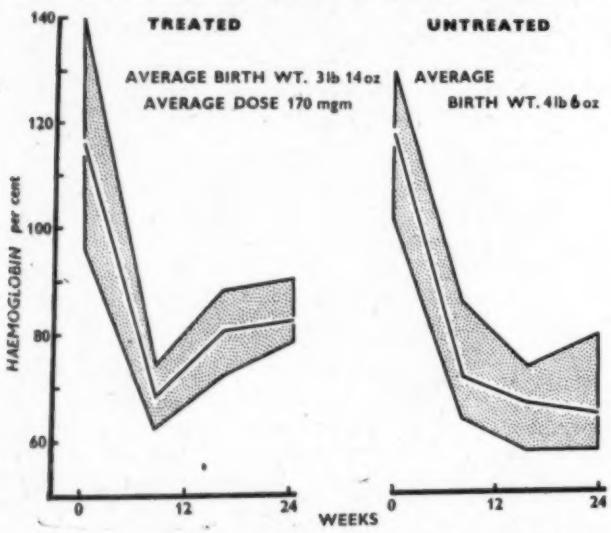

FIG. 5.—Anaemia of prematurity. Effect of the prophylactic use of intramuscular iron.

Marrow biopsies of the tibiae were carried out on some of the infants before treatment and on all of them at 16 weeks. No sideroblasts were seen in the specimens obtained before treatment, but were present in those examined at 16 weeks after treatment, varying between 6 and 10% of the total nucleated red cells seen.

In this group were included two sets of twins, and one of each pair was treated, the results being shown in Fig. 6.

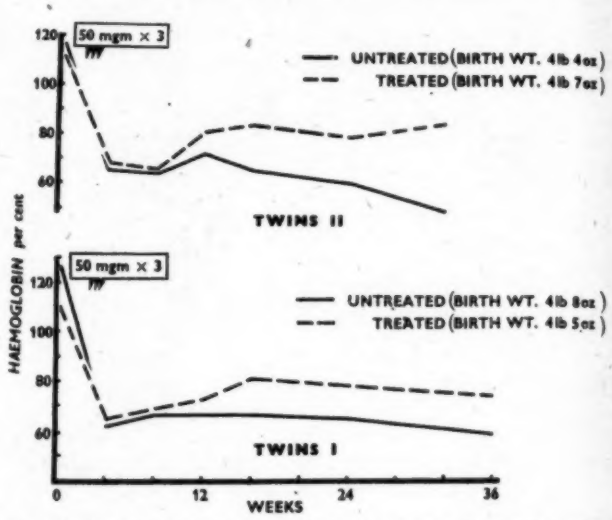
50 mgm x 3
UNTREATED (BIRTH WT. 4 lb 4 oz)
TREATED (BIRTH WT. 4 lb 7 oz)
TWINS II
50 mgm x 3
UNTREATED (BIRTH WT. 4 lb 8 oz)
TREATED (BIRTH WT. 4 lb 5 oz)
TWINS I
HAEMOGLOBIN per cent
WEEKS

FIG. 6.—Twins, treated and untreated. Effect of prophylactic treatment.

Surgical Cases

There were 10 cases in this group, and although all showed dramatic improvement the surgical conditions were too varied to allow of a detailed analysis. Injections were given both pre-operatively and post-operatively, and with effect occasionally instead of transfusion. For example, two infants with harelip were given 300 mg. of iron pre-operatively: one, a year old, had a haemoglobin of 68%, which fell to 50% after the operation, but had reached 74% four weeks later; the other, aged 8 months, with a haemoglobin of 54% pre-operatively, reached 84% at five weeks. An infant with a bleeding rectal polyp whose haemoglobin was 52% was given 200 mg., and two weeks later his haemoglobin was 95%.

Discussion

There is no doubt that this preparation produces a rapid clinical and haematological response and that the improvement is maintained for many months. Infections, both

TABLE III.—*Anaemia of Prematurity—Prophylaxis*

	Untreated									Treated								
	Birth Wt.	Haemoglobin %								Birth Wt.	Haemoglobin %							
		Initial	Weeks								Initial	Weeks						
	lb. oz.		4	8	12	16	20	24		lb. oz.		4	8	12	16	20	24
1	4 8	128	62	66	66	66	—	64	1	4 5	110	64	68	72	80	—	78
2	4 4	118	66	64	72	64	60	60	2	4 7	114	68	66	80	84	—	78
3	4 4	102	92	86	86	74	58	64	3	3 12	96	—	62	72	68	86	—
4	4 13	112	86	64	70	—	86	80	4	3 5	98	—	70	74	86	80	78
5	3 14	102	82	78	74	58	60	60	5	4 1	134	64	66	84	76	74	86
6	3 15	—	92	—	74	68	—	76	6	4 5	128	—	72	84	86	88	90
7	4 12	130	—	—	—	66	—	60	7	3 2	—	—	—	78	74	86	84
8	4 6	130	96	70	—	74	—	62	8	3 7	140	90	—	80	76	—	80
9	4 11	126	—	86	86	—	—	72	9	4 2	116	86	74	70	88	82	82
10	4 7	—	—	64	64	—	—	58	10	4 2	116	—	—	—	—	—	84
Average:	4 6·2	118·3	82·3	72·2	74·0	67·1	66·0	65·6		3 14·4	116·8	74·4	68·3	77·1	79·7	82·7	82·2

Difference of means: Initial 1.7%: $0.5<p<0.6$. 8 weeks 3.9%: $0.2<p<0.3$. 16 weeks 22.6%: $p<0.01$. 24 weeks 26.6%: $p<0.01$.

in medical and in surgical conditions, prevent the utilization of parenteral iron just as they do when oral iron is used in such cases, and, furthermore, when used in infants with an infection reactions are more likely. The adverse effect of infection during treatment is illustrated by infant No. 12 in Table II. No more than the amount calculated to make good the iron deficit should be given.

This dose was calculated from the formula :

Fe required in mg. = 1.31 × (17 − Hb in g.) × Wt. in lb.

The 1.31 is a constant based on the iron content of haemoglobin (0.34%), which gives 20 mg. of Fe per lb. at a haemoglobin level of 14.8 g.%. $\frac{20}{14.8}$ = 1 31, and is the number of mg. of Fe required to raise the haemoglobin 1 g. per 100 ml. for each pound of body weight. The figure 17 was chosen arbitrarily to allow for depleted iron stores (14.8 + 2.2). This was later increased to 19 with even better and more rapid response as more complete saturation of the tissues was obtained.

The injections, given deeply, were not unduly painful and the discomfort was short-lived. No staining of the skin occurred. The upper and outer quadrant of the buttock is the most suitable site in infants ; the arm is not suitable and the thigh less so than the buttock. No pyrexia or other side-effect was noticed. Injections were given to in-patients or out-patients daily, on alternate days, or weekly, as was convenient. A few in-patients received two injections a day—that is, 100 mg. of Fe—thus considerably reducing their stay in hospital, which is an important point in the age group concerned.

The average rate of response was between 1.4 and 1.5% haemoglobin a day, which is better than Dickstein and his colleagues obtained—which was 1% a day, using intravenous iron. Imferon contains two and a half times more iron than the usual saccharated iron oxide preparations ; larger doses of elemental iron can therefore be given at each injection. This is shown by the very rapid response during the first two weeks of treatment. In the nutritional anaemia cases the average increase was 20.6% and in the treated anaemia of prematurity 20.3%. The over-all increase in haemoglobin was 32% in the nutritional anaemias and 28% in the anaemias of prematurity. Hanna and Shehata (1951) found an average increase of 30% in 35 cases treated with intravenous iron, and noted that the more severe the anaemia the more rapid the response—a finding we also observed, the average daily increase in our infants whose initial haemoglobin was below 50% being 2%. This swift response is due to the very rapid absorption of the iron from the tissues, as shown in Fig. 7, which illustrates the appearance of iron in the marrow of an infant within 48 hours of a 50-mg. injection.

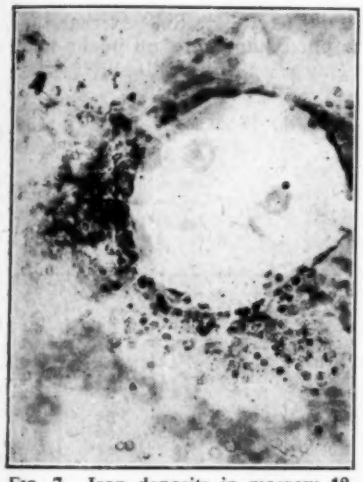

FIG. 7.—Iron deposits in marrow 48 hours after injection of 50 mg. of imferon. (×160.)

The actual utilization was not calculated, but is obviously very high. An increase of approximately 12% Hb was obtained for 100 mg. of iron injected, whereas only 4% is the calculated increase in adults, although adults and infants cannot be strictly compared in this respect.

Thrombosed veins, syncope, and other side-effects were reported in about 10% of all the series treated with intravenous iron, and, of course, accidental extravenous injection of the saccharated iron oxides is very painful, and damaging to the tissues. No side-effects were noted in any of our cases.

The indications for parenteral iron are limited. Hagberg (1951) concluded that it was indicated in cases of intestinal disorders such as coeliac disease or ulcerative colitis, and in any patient with nausea and vomiting.

It is particularly useful for infants whose home conditions are poor and who otherwise would have to be admitted to hospital for treatment, and for those infants in whom more rapid haemoglobin regeneration is required than can usually be obtained by oral therapy. Dickstein and his colleagues pointed out that a course of intravenous iron could often replace a blood transfusion and so reduce the risks attached to transfusion, although the technique, involving venepuncture, is similar in both. In our series there were premature twins who attended the clinic at the age of 10 months, obviously anaemic and with hepatosplenomegaly. One had a congenital heart lesion, and for this reason we preferred intramuscular iron to transfusion ; he was given 300 mg. of imferon. His haemoglobin, 38% on admission, rose to 80% in two weeks. The second was transfused (with 200 ml. of blood), and the haemoglobin rose from 34% to 60%, where it remained. Thereafter he too was given iron (100 mg.), and his haemoglobin reached 80% two weeks later ; the twins then progressed in parallel.

With reference to the use of blood transfusion in premature infants in order to prevent anaemia, Wolman (1953) stated that, although there were certain objections to transfusion, these were " counterbalanced by the general clinical impression that transfusions, when given to subthreshold infants, improve the general nutritional status, rate of weight gain, and perhaps resistance to infection." Rossier and Potiron (1955), after a five-year study, conclude that " repeated and systematic transfusions are the only efficient method of preventing the anaemia of prematurity and are the sovereign remedy for the cure of such anaemia—early or late and from whatever cause the prematurity occurred." We consider that this new preparation which we are describing here makes the foregoing conclusion no longer justified.

The use of intramuscular iron gives all the advantages of transfusion or intravenous iron therapy without the disadvantages.

Summary

An iron-dextran complex—" imferon "—has been given intramuscularly to more than 100 anaemic infants, with marked and rapid haematological and clinical improvement. The haemoglobin levels have been maintained for several months. The preparation has also been successfully used in the prevention of the anaemia of prematurity and in surgical cases complicated by haemorrhage, and pre-operatively to supply extra iron when operative bleeding is likely to be severe.

It is easy to give, and, provided the amount calculated to be equivalent to the iron deficit is not exceeded, is free from unpleasant reactions. It can be given in the out-patient department or the home, and thereby obviate admission to hospital in many cases. It can occasionally replace transfusion. Although it should not be used instead of oral iron as a routine procedure, it is a valuable addition to the therapy available for the treatment of severely anaemic infants or those intolerant of, or resistant to, oral iron preparations.

We are indebted to Dr. F. Fletcher for his help and advice throughout the course of this study and to Messrs. Bengers for supplying the imferon. We are also indebted to Dr. H. B. Marsden, pathologist, Royal Manchester Children's Hospital, who did all the haemoglobin estimations and reported on the marrow smears from the infants at that hospital; and to

colleagues on the staff of the hospital and to Dr. D. Macaulay, physician, Duchess of York Babies Hospital, for permission to include some of their cases.

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METABOLIC CHANGES AND THERAPEUTIC CONSIDERATIONS IN BILATERAL ADRENALECTOMY

BY

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The profound metabolic and circulatory changes produced by surgery and anaesthesia have been intensively studied in recent years. The metabolic aspect, in particular, has been investigated by Moore and Ball (1951), who correlated data of other workers in this field. The consensus of opinion is that hyperactivity of the adrenal cortex is responsible for the broad pattern of these changes.

The superimposition of bilateral adrenalectomy upon a surgical procedure would thus produce further problems and difficulties to the body economy worthy of study.

Clinical Material and Methods

Three consecutive patients with carcinoma of the breast and widespread metastases admitted for simultaneous bilateral adrenalectomy and oophorectomy were considered. Each had had a radical mastectomy; all had been treated with prolonged androgen therapy.

After haemoglobin, protein, and electrolyte deficiencies had been corrected, the patients were prepared for operation by the regime advocated by Hollander *et al.* (1952). The details of cortisone, deoxycortone acetate (D.C.A.), and salt administration, which were started the day before the operation, are shown in Fig. 1. Each patient was taking fluid by mouth on the first day after operation and a normal diet on the seventh day. Accurate fluid balance charts were kept throughout the patients' stay in hospital.

The investigation started two or three days before the operation and lasted until the patients were discharged three weeks later. Urine analysis included volume, specific gravity, sodium, potassium, chloride, creatinine, urea, and ammonia. Routine clinical laboratory methods were used throughout, save for creatinine, which was estimated by the method advocated by Brod and Sirota (1948). The glomerular filtration rate was calculated as 24-hour endogenous creatinine clearance. The percentage excretion of water, sodium, and potassium was calculated according to the method of Platt (1950). The potassium/nitrogen ratio was calculated from the sum of the urea, ammonia, and creatinine nitrogen found in the 24-hour urine specimen.

Blood chemistry included haematocrit and the plasma content of sodium, potassium, chloride, CO_2 combining power, creatinine, and urea. The intracellular sodium, potassium, and chloride were calculated from the formula:

$$C_c = \frac{C_b - C_p\,(1-Ht)}{Ht}$$

where C_c, C_b, and C_p are the concentrations of sodium, potassium, or chloride in the cells, whole blood, and plasma respectively in mEq/litre, and Ht is the haematocrit expressed as a fraction of whole blood. Since the completion of this paper it has been brought to our attention that a similar formula, but with an obvious printer's error, had been derived by Eliel and Pearson (1951).

Results

Our results after adrenalectomy are similar in pattern to, but different in detail from, those found in non-adrenalectomized patients after surgery and anaesthesia. The data are presented in three phases.

(1) Period of Sodium Retention

On the first day after the operation the concentration of urinary sodium was decreased in one patient and was the same as the controlled pre-operative level in two. After this the concentration of sodium in the urine decreased in the subsequent 24-hour periods, reaching its minimum value approaching zero in two patients on the fifth day, and in one patient on the third day after operation—average four days (Figs. 1 and 2). The potassium excretion in the three patients averaged 44 mEq/day for the first three days after

TABLE I.—*Case* 3, *aged* 56. *Bilateral Adrenalectomy and Oophorectomy. Detailed Constituents of the Three Periods of Sodium Excretion*

	Day	Urine Vol. ml./ 24 hr.	Sp. Gr.	% Excretion Na*	% Excretion K†	% Excretion H_2O‡	G.F.R.Cr. ml./24 hr.	K/N Ratio
	−1	1,380	1·016	1·35	23·5	2·45	39	6·2
	0	Operation						
Period of Relative Na Retention	1	500	1·030	0·60	23·6	1·36	32	6·5
	2	790	1·022	0·20	24·2	1·16	62	5·5
	3	500	1·024	0·07	21·2	0·98	42	4·0
	4	1,215	1·012	0·05	11·5	0·95	97	3·1
	5	560	1·012	0·14	17·0	1·14	39	4·2
Period of Early Na Diuresis	6	1,475	1·010	0·32	15·0	1·46	94	3·8
	7	1,255	1·012	0·56	20·8	1·46	69	4·9
	8	1,405	1·008	0·90	8·0	1·76	68	2·1
	9	1,480	1·010	1·00	12·5	2·12	54	3·0
	10	1,740	1·012	1·82	15·2	2·24	65	3·8
	11	1,905	1·012	1·55	17·4	2·27	69	
§ Period of Relative Na Retention	12	1,865	1·012	0·95	19·0	1·86	84	4·9
	13	2,350						
	14	1,640	1·008					
	15	1,340	1·010	0·70	15·5	1·50	75	4·6
Period of Late Na Diuresis	16	1,655	1·020					
	17	1,380	1·014	0·72	21·2	1·40	81	6·1
	18	1,580	1·016					
	19	1,630	1·014					
	20	1,630	1·012	0·92	24·5	1·80	77	6·6
	21	1,330	1·012	0·91	24·2	1·62	67	7·3
	22	1,115	1·013	0·91	22·0	1·48	63	5·6
	23	2,695	1·012	2·25	23·2	2·86	62	5·8
	24	1,800	1·014	1·80	23·0	2·33	58	
	25	2,500	1·008	2·33	35·0	3·50	60	4·3
	26	2,100	1·013	1·95	31·0	2·56	69	4·9
	27	2,000	1·013				61	6·0
	28	2,625	1·014				79	9·5
	29	1,405	1·016				78	
	30	1,620	1·008					

* $\frac{U.Na}{P.Na} \times \frac{P.cr.}{U.cr.} \times 100$. † $\frac{U.K}{P.K} \times \frac{P.cr.}{U.cr.} \times 100$. ‡ $\frac{P.cr.}{U.cr.} \times 100$.

§ The period of relative sodium retention occurred in all three patients. It may, however, be the result of random variation rather than a true period, characteristic of adrenalectomized patients (see Table III and discussion).

TABLE II.—*Case 2. aged 43. Bilateral Adrenalectomy and Oophorectomy*

Day		Urine Vol. ml./ 24 hr.	Sp. Gr.	% Excretion Na*	% Excretion K†	% Excretion H_2O‡	G.F.R. Cr. ml./min.	K/N Ratio
Pre. Op. Period	−3	1,240	1·008	1·37	13·3	2·75	37	3·8
	−2	1,500	1·006	1·50	21·5	3·60	39	5·2
	−1	653	1·010	1·71	25·0	2·50		6·4
	0			Operation				
Period of Na Retention	1	1,240	1·017	0·51	18·6	1·05	78	
	2	1,830	1·012	0·01	12·2	1·05	120	2·9
	3	1,540	1·010	0·05	12·2	1·60	85	2·9
Period of Early Na Diuresis	4	1,600	1·009	0·28	14·5	1·75	85	4·1
	5	1,290	1·009	0·25	12·2	1·85	60	3·8
	6	1,135	1·009	0·42	11·5	1·90	55	3·0
	7	1,050	1·008	0·97	12·8	2·00	46	
	8	1,700	1·010	0·91	10·7	1·65	59	3·1
	9	1,700	1·010	1·24	12·6	2·20	64	4·0
Period of Late Na Diuresis	10	1,550	1·008	1·21	28·7	2·00	67	8·7
	11	1,500	1·011	1·17	22·2	1·45	88	7·3
	12	1,340	1·010	1·78	31·3	2·20	52	8·7
	13	1,420	1·010	1·20	36·7	2·10	62	9·0
(Period of Relative Na Retention	14	1,400	1·009	1·39	19·5	2·30	54	4·4
	15	2,040	1·006	1·13	19·5	2·60	70	5·4
	16	1,970	1·010	1·04	19·6	2·00	90	4·7
	17	2,250	1·009	1·52	16·0	2·50	75	5·3

* $\frac{U.Na}{P.Na} \times \frac{P.cr.}{U.cr.} \times 100$. † $\frac{U.K}{P.K} \times \frac{P.cr.}{U.cr.} \times 100$. ‡ $\frac{P.cr.}{U.cr.} \times 100$.

§ The period of relative sodium retention interrupts the period of late diuresis.

operation, and 55 mEq/day for the whole period of sodium retention, as against 45 mEq/day in the pre-operative period. During the period of sodium retention the specific gravity of the urine increased and was considerably higher than in the pre-operative period. In two patients the urine volume reached pre-operative values on the first day after operation, and in the third patient only on the fourth day.

There was a marked decrease in the percentage of water and sodium excretion on the first day after operation, while the percentage figure of potassium excretion remained at or slightly below pre-operative values. These values decreased until the peak of sodium retention on the fourth day after operation and then slowly approached pre-operative values on the ninth and tenth day after operation. The creatinine clearance in the pre-operative period in our patients averaged 38.5 ml./min. There was a marked increase in the glomerular filtration rate to double this value during this period. The glomerular filtration rate varied with the urine flow.

The potassium/nitrogen ratio averaged 5.9 during the pre-operative phase. After operation it was reduced, and remained below the pre-operative value until late into the sodium diuresis phase. This fall in potassium/nitrogen ratio in the early days after operation was maintained in spite of liberal salt supplementation (Tables I and II).

During the same period the nitrogen excretion rose from a pre-operative average of 8.5 to 21.9 g. a day, indicating an increased catabolic process.

In each patient the plasma sodium fell during the period of sodium retention (Fig. 2). In two of the three patients studied the plasma potassium fell below the pre-operative level, and hypokalaemic alkalosis developed. At the same time the blood urea rose sharply above the pre-operative

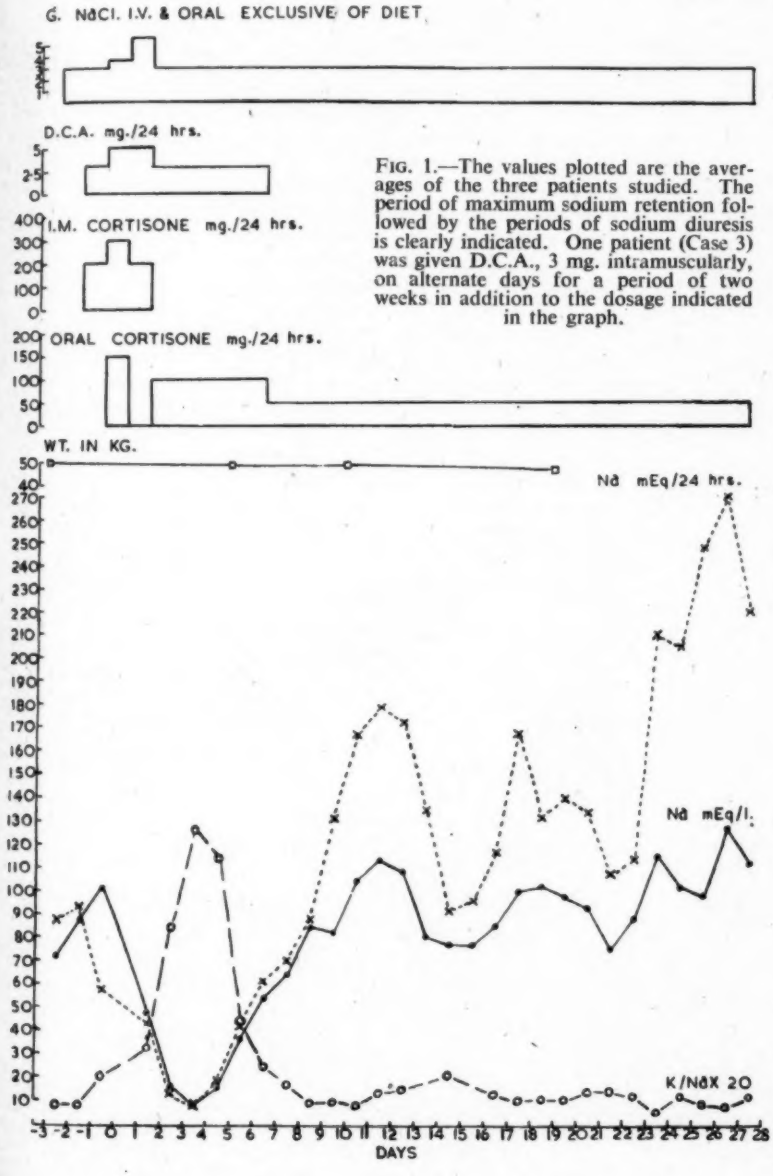

FIG. 1.—The values plotted are the averages of the three patients studied. The period of maximum sodium retention followed by the periods of sodium diuresis is clearly indicated. One patient (Case 3) was given D.C.A., 3 mg. intramuscularly, on alternate days for a period of two weeks in addition to the dosage indicated in the graph.

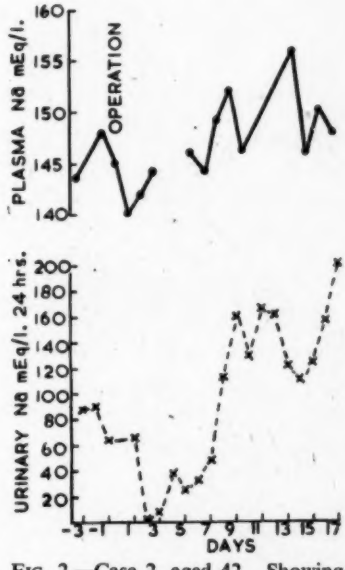

FIG. 2.—Case 2, aged 42. Showing the paradoxical relationship between the plasma sodium levels and urinary excretion of sodium. The plasma level of sodium rises as the excretion of sodium rises and falls when the urinary excretion of sodium falls. This phenomenon was noted during the period of sodium retention in patients undergoing surgical procedures other than adrenalectomy (Moore and Ball, 1951). In our patients this "paradoxical sodium level" persisted throughout the period of study.

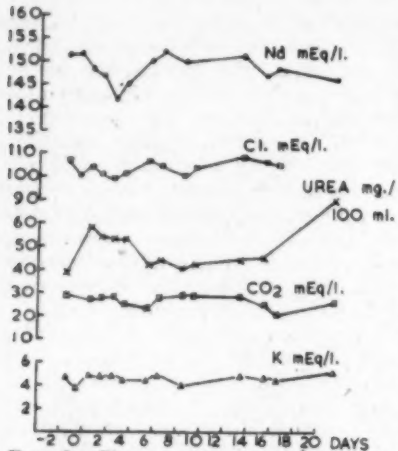

FIG. 3.—Plasma electrolyte changes in Case 1 following bilateral adrenalectomy and oophorectomy.

level in each patient, and remained elevated until the peak of sodium retention was reached, and then fell to normal with the onset of diuresis.

The rise in blood urea, simultaneous with the fall in haematocrit value, in the face of an increased glomerular filtration rate and increased excretion of urea is another indication of increased catabolism (Fig. 3).

(2) Period of Early Sodium Diuresis

In the period of early sodium diuresis the glomerular filtration rate is double pre-operative values and still tends to follow the volume of urine excreted (Tables I and II). The percentage excretion of water, sodium, and potassium tends to remain slightly below the pre-operative level. The potassium/nitrogen ratio is well below the pre-operative level during this early period of sodium diuresis. A sodium excretion of over 200 mEq/day recorded in one patient, and over 150 mEq/day in the other two, was in fact accounted for by the increased glomerular filtration rate.

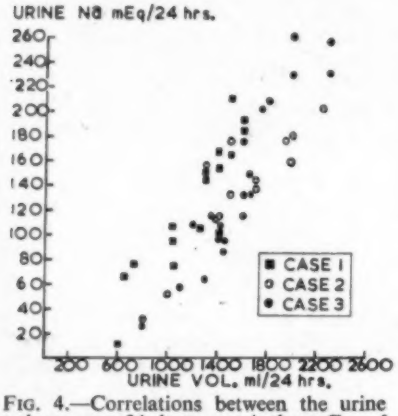

FIG. 4.—Correlations between the urine volume per 24 hours and the mEq of sodium excreted during the periods of sodium diuresis in the three patients studied. The similarity to the data obtained by Burston and Garrod (1952), who studied the relation between urine volume and daily chloride excretion in patients with Addison's disease adequately treated with cortisone, is striking.

(3) Period of Late Diuresis

The period of late sodium diuresis is characterized by an increase in the percentage excretion of water, sodium, and potassium equal to or above the pre-operative figures, with a maintenance of the high glomerular filtration rate. The potassium/nitrogen ratio during this period rose to above the pre-operative level and to values much higher than those found during the early phase of sodium diuresis. During the late phase of diuresis the glomerular filtration rate still follows, but not as strictly as in the earlier periods after operation, the volume of urine excretion. It will be noted that there is a tendency for the urine specific gravity to rise with increased urine flow (Tables I and II).

During both periods of sodium diuresis the urine sodium concentration and the amount of sodium excreted in 24 hours is proportional to the urine flow (Fig. 4).

During the periods of sodium diuresis the plasma sodium levels increased. In Case 2 the plasma sodium rose from a level of 140 mEq/l. at the peak of sodium retention to 153 mEq/l. in the phase of early sodium excretion, and to 156 mEq/l. during the peak of late sodium diuresis. A similar pattern was followed in the other two patients (Fig. 2).

The blood urea returned to the pre-operative level during the phase of early sodium diuresis, but rose above the pre-operative values in the late phase of sodium diuresis (Fig. 3).

Intracellular Sodium and Potassium

The shift of sodium and potassium across the red blood cell membrane is consistent with the paradoxical plasma sodium values (Table III).

During the period of sodium retention the sodium content of the red blood cell remains constant or below pre-operative values. At the same time there is a sharp fall in the haematocrit reading.

During the period of sodium diuresis the concentration of intracellular sodium is markedly reduced. This coincides with the raised plasma sodium found during this period.

During the brief periods of late sodium retention which punctuate the period of sodium diuresis the intracellular sodium is raised coincidently with a fall in plasma sodium. The intracellular potassium concentration is reciprocal with the sodium changes.

Discussion

The fact that patients subjected to adrenalectomy and patients subjected to operations other than adrenalectomy develop a similar urinary excretion pattern of sodium retention and increased potassium and nitrogen excretion suggests that in both groups anaesthesia and operation occasion a primary metabolic disturbance. This results in the enlargement of the extracellular space and a consequent fall in haematocrit reading and plasma sodium (Elman *et al.*, 1949; Wilkinson *et al.*, 1951; Conway and Hingerty, 1953).

After an operation other than adrenalectomy the patient reacts to this disturbance by adrenocortical hyperactivity (Moore and Ball, 1951; Elman *et al.*, 1952).

The reversal of the potassium/sodium ratio is characteristic of adrenocortical activity on the kidney tubule (Tait *et al.*, 1952; Elman *et al.*, 1952). Elektrocortone (Von Pesaulles *et al.*, 1953) or aldosterone (Simpson *et al.*, 1953) causes a renal leak of potassium, together with sodium retention. The reversal of potassium/sodium ratio in our patients is effected by a constant excretion of potassium compared with pre-operative values, and an increase in sodium retention. It has been suggested by Winter *et al.* (1938) that the posterior pituitary is responsible for the fall of serum

TABLE III.—*The Data Listed under Period of Relative Sodium Retention is a Composite Compiled from such Periods Regardless of whether they Occurred in the Period of Early or Late Diuresis*

	Case No.	Pre-op. (Days)			Period of Early Na Retention (Days)				Period of Early Na Diuresis (Days)							Period of Relative Na Retention (Days)			Period of Late Na Diuresis (Days)	
		3	2	1	2	3	4	5	1	2	3	4	5	6	7	1	2	3	1	2
Haematocrit ..	1	40	35	40	40	35	35	33	35	35	34			34	34	33	33	33		34
	2		40	40	40	35	34			34	34	34	33	37				34	34	33
	3		48	49	49	49	39	40	40		44	44	41	38			38			44
Intracellular Na (mEq/l.) ..	1		23	18	5	10	18	24	18	8	7			17·5	22·5	30	30	36		6
	2			19	19	19	19		5	5	6						19			1
	3		24	15	10	8	16				0	7	0				13			0
Intracellular K (mEq/l.) ..	1	111	115	110	113	102	105	105		113	112			110		114	114	117		115
	2			104	104	105	105	105		117	114	108						108	105	117
	3	106	106	106	103	106					109	106	106	110			106			113

sodium after operation. LeQuesne and Lewis (1953), LeQuesne (1954), and Dudley *et al.* (1953) have shown that there is a brief period, of some hours, of sodium and water retention with a urine of high specific gravity after operations other than adrenalectomy, and that this is the result of an increased posterior pituitary activity. Then follows a normal or increased production of urine which is characteristic of marked adrenocortical activity. Elman *et al.* (1949) reported after operations other than adrenalectomy a decrease in urinary specific gravity on the first day which persisted for several days in spite of a daily fluid intake of 2,000 ml. Our patients showed an increased urinary specific gravity during the complete period of sodium retention which lasted up to five days, in spite of an adequate urine output (Tables I and II).

The prolonged period during which the specific gravity of the urine of our patients remained high on an average intake of 2,200 ml. of water a day could be explained by the increased percentage water retention (pitressin), a simultaneous increased glomerular filtration rate (cortisone), plus a salt-retaining factor. The latter is under investigation. It may well be due to the anterior pituitary (Stein *et al.*, 1952) or pitressin itself (Hollander *et al.*, 1952). This combination of hormones would thus simulate increased adrenocortical activity by producing an adequate volume of urine with a high K/Na ratio.

Moore and Ball (1951), Elman *et al.* (1952), and Randall *et al.* (1949), writing on post-operative potassium deficiency in patients after surgery other than adrenalectomy, stated that the rise in potassium/nitrogen ratio in their patients was the result of increased adrenocortical activity. In our patients the potassium/nitrogen ratio fell. After the first three days following operation our patients were not on a controlled nitrogen diet. However, since ordinary dietary variations can only cause an increased potassium/nitrogen ratio, the low potassium/nitrogen ratio found in our patients is taken to indicate an absence of adrenocortical activity. That a profound catabolic process did occur during the phase of sodium retention is indicated by the threefold increase in nitrogen excretion during this period.

Fourman (1952) has shown that D.C.A. produces a fall in serum sodium and an expansion of the extracellular space in patients with Addison's disease. Conway and Hingerty (1953), studying rats after bilateral adrenalectomy, recorded a decrease in serum sodium after operation which was greatly magnified by the administration of D.C.A. but abolished by cortisone. It would seem that the use of D.C.A. in the period of sodium retention is unnecessary or may even be harmful. Should the decrease in plasma sodium indeed be the prime mover in causing sodium retention, D.C.A. could prolong the period of sodium and water retention at a time when catabolic processes are increased. Butler *et al.* (1953) studied two cases of bilateral adrenalectomy, one with and one without D.C.A., and drew the clinical impression that D.C.A. was unnecessary. Kreiger *et al.* (1953) studied five patients and accords with this view. We have since this study observed three patients subjected to adrenalectomy without D.C.A., and noted that the mineral excretion pattern was identical with this series.

The close relationship between the glomerular filtration rate and the 24-hour urine volume during the period of sodium retention in our patients resembles the findings of Burston and Garrod (1952), who established this direct relationship between glomerular filtration rate and urine flow in patients with Addison's disease before treatment with cortisone. Treatment with cortisone in their patients raised the glomerular filtration rate and established a direct linear relationship between urine flow and chloride output. A relationship of this kind was present in our patients in the late diuretic phase (Fig. 4). Thus our patients resemble cases of Addison's disease with inadequate cortisone therapy in the phase of sodium retention and the picture of adequate cortisone therapy in the phase of late diuresis, although the actual cortisone dosage administered was less in this phase (50 mg. per 24 hours) than in the phase of sodium retention (100 to 200 mg. per 24 hours).

That cortisone and antidiuretic substance (A.D.S.) can be antagonistic has been demonstrated (Eversole *et al.*, 1942; Hollander *et al.*, 1953). This relationship between A.D.S. and cortisone might explain the Addisonian features of the glomerular filtration rate noticed in our patients. It is also of clinical importance. A persistent low blood pressure, together with a scanty urine of high specific gravity, and especially if accompanied by abdominal pain, a raised temperature, high pulse rate, and vomiting, indicates inadequate cortisone therapy regardless of the sustaining dosage. We have seen four patients after operation with hypotension who did not respond to noradrenaline but who did respond to intravenous hydrocortisone.

The adrenalectomized patient differs from other surgical patients in that no period of convalescence restores a normal hormonal balance. Instead, a state is reached which is reminiscent of Addison's disease, modified by the administration of cortisone. The cortisone has the renal effect of increasing the glomerular filtration rate while maintaining the percentage excretion rate of water, sodium, and potassium above that of the earlier periods after operation.

The consequent excessive loss of sodium in proportion to urine flow is not reflected by the plasma sodium level, which remains high by reason of the shift of intracellular sodium into the extracellular space. The serum potassium, however, does fall. Large amounts of sodium may thus be lost without detection. The use of D.C.A. or the newer fluorohydrocortisone may prove beneficial in the late diuretic phase.

Conclusions and Summary

Patients undergoing major surgical operations other than total adrenalectomy show metabolic changes which are ascribed to adrenocortical hyperactivity. These are sodium retention, increased potassium excretion, high potassium/nitrogen ratio, and low specific gravity urine. The post-operative adrenalectomized patient mimics those metabolic changes. In the absence of adrenal glands these metabolic changes effected by increased pituitary activity modified by cortisone therapy are sodium retention, a constant potassium excretion, low potassium/nitrogen ratio, and high specific gravity urine.

Surgical patients other than those undergoing bilateral adrenalectomy enter a phase of diuresis after the period of sodium retention and then return to a normal preoperative metabolic pattern. Adrenalectomized patients enter a phase of permanent sodium diuresis which is not unlike that of patients with Addison's disease adequately treated with cortisone.

The use of D.C.A. is probably unnecessary in the immediate post-operative period and may even be harmful. The use of D.C.A. in the period of sodium diuresis is discussed.

Adrenalectomized patients have an increase of antidiuretic substance in the blood; this substance is antagonistic to cortisone. Signs of adrenal insufficiency, low blood pressure, abdominal pain, and scanty urine with high specific gravity and low sodium content demand increased cortisone therapy regardless of the maintenance dose.

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BILATERAL ANTERIOR TRANSABDOMINAL ADRENALECTOMY

BY

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Bilateral adrenalectomy is probably not destined to remain a standard operation even for advanced and hopeless cancer of the breast, but exposure of the adrenal glands, and some form of bilateral adrenalectomy, is likely to remain a standard procedure for at least some varieties of adrenal disease. In both circumstances an anterior approach has many advantages. In adrenalectomy for cancer it is often dangerous to turn the patient to the prone position if the cervical spine is the seat of advanced disease; a hemiplegia has sometimes been produced by this change in position. When a patient undergoing adrenalectomy for cancer has a pathological fracture of the femur, the prone position is sometimes, at least, awkward. When the adrenal glands are exposed for disorders of adrenal function or for the suspicion of adrenal tumour, it is extremely convenient to present both adrenals simultaneously to close inspection, and this is possible in all cases, even if the actual removal of the right adrenal gland from the front proves to be difficult, as it sometimes does. The left adrenal can always be removed with greater facility from the front than from the back, and even if the right adrenal, having been clearly inspected, proves impossible of removal from the front, as it has not done in our hands, nothing would be lost then in removing it, or the greater part of it if that were desired, from the back.

Route of Approach

When the operation is done for advanced cancer, bilateral oophorectomy is usually done at the same time, and it is then convenient to explore the upper abdomen directly without change of the patient's position. The left adrenal is exposed and removed; the right adrenal is explored also. Theoretically, if the removal of the right adrenal offered insurmountable difficulty there would be no objection to closing the abdominal wound, turning the patient over, and completing the operation on the right side from behind. We have not found it necessary to do this in 12 successive cases in which we have performed the bilateral operation from the front. This anterior approach has two particular advantages in cancer cases. The upper abdomen can be fully explored for metastases, and outlying islands of adrenal tissue, separate from the main gland, may easily be recognized and removed. On two occasions we have found accessory adrenal tissue in a low position in the retroperitoneum, where it would not have been detected by a posterior approach. The anterior approach gives a clear view of the retroperitoneal space on both sides.

Having now had experience of the anterior route, the posterior route, and the postero-lateral route, we can say that any of these routes may on occasion prove difficult, and we have not had greater difficulty with the anterior abdominal approach than with the posterior and postero-lateral operations. Indeed, it has been possible, when the operation has been performed from the front, to be more certain of removing both adrenal glands intact, with their borders and surfaces unbroken, and this is always a great assurance that the adrenalectomy has been complete. Left anterior adrenalectomy is a simple abdominal operation. In most, though not in all, cases right anterior adrenalectomy is a simple abdominal operation also. The advantages of the anterior route compensate for the technical difficulties which are sometimes met on the right side.

When the operation is performed for adrenal dysfunction, bilateral *subtotal* adrenalectomy is always possible and usually easy by way of the abdomen, and it is satisfying in such circumstances to have both adrenal glands displayed at the same time. When any other approach is used one never knows, before performing subtotal adrenalectomy on one side, whether there may not be a tumour in the other gland still to be explored. The simultaneous exposure of the adrenal glands by two separate posterior incisions is awkward and dissatisfying. When an adrenal tumour is suspected, the advantage again of exposing both adrenal glands simultaneously is very substantial and the removal of a tumour from either gland is always easily possible through the abdomen.

There are two details of operative procedure which facilitate the anterior operation. On the right side, mobilization of the spleen with the splenic vessels and the left end of the pancreas brings the left adrenal gland into clear view. On the right side, care is taken to draw down the kidney before opening the retroperitoneum; this usually fixes the adrenal *in situ*. If the peritoneum is opened, and the kidney *then* retracted downwards, the suprarenal does not always follow it. Indeed, it sometimes does not move down with the kidney at all.

Operative Detail

The incision is an oblique one parallel with and one handbreadth below the right costal margin. From a point just lateral to the right border of the right rectus muscle, the incision is carried upwards and to the left to meet the left costal margin. The right rectus and its sheath are divided in the line of the incision, the linea alba is divided in the midline, and the left rectus and its sheath are divided also as far as the costal margin. The peritoneal cavity is opened. The spleen is mobilized as for splenectomy by an incision through the peritoneum just beyond its reflection from spleen to abdominal wall (left or posterior layer of the lineal renal ligament). The retroperitoneal continuation of the transversalis fascia is divided in the same line, and the spleen is drawn forward and to the patient's right with the tail and body of the pancreas and the splenic vessel (Fig. 1). This immediately brings the left adrenal gland to

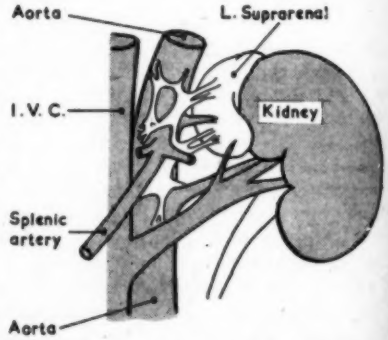

FIG. 1.—Traction on splenic artery fixes aorta, drawing it forwards and to patient's right, with renal artery, suprarenal artery, suprarenal nerves, and suprarenal gland.

clear view. If traction is maintained on the spleen, pancreas, and splenic vessels the tension on the splenic artery is transmitted to the coeliac axis and consequently to the aorta and renal artery, and the adrenal vessels and sympathetic nerves, and so the adrenal gland itself, are fixed. This manœuvre may alter the position of the gland, to the operator's advantage, by 3–4 cm. (Fig. 2). The gland can then be dissected under vision, its vessels ligated, and the gland removed entire. The retroperitoneum in the area is then inspected for the presence of accessory adrenal tissue.

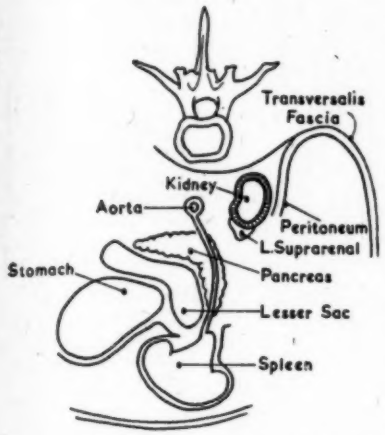

FIG. 2.—Spleen mobilized with splenic vessels and pancreas to expose left suprarenal gland.

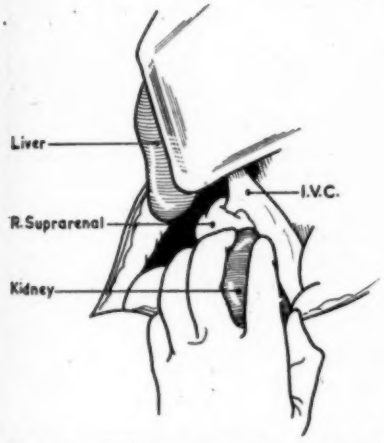

FIG. 3.—Kidney manually retracted downwards, liver upwards, inferior vena cava to patient's left. Right suprarenal gland exposed.

Attention is now turned to the right side, and the right adrenal is sought in the area bounded by the lower border of the right lobe of the liver, the right edge of the vena cava, the upper border of the renal vessels, and the upper pole of the right kidney. If the liver is bulky or situated in a particularly low position, it is helpful to divide between forceps the falciform ligament and the right triangular ligament. A retractor is gently inserted to draw the liver upwards. This retraction must be carefully done, for the liver in this particular situation is easily torn. The upper pole of the kidney is then depressed by two fingers; one, placed medially in relation to the upper pole, pressing downwards on the renal artery, and the other on the outer edge of the upper pole. When this has been done, an area of peritoneum a few centimetres in diameter is excised from the hepato-renal pouch. Incision of this peritoneum is not sufficient: the edges of such an incision do not always separate well. When this patch of peritoneum has been removed the adrenal gland comes under vision. Vision is improved by rolling the patient over a little towards her left side.

A retractor can now be inserted to roll away gently the right edge of the vena cava. The outer border of the gland is first dissected free, and then the inner border is freed by careful division between ligatures of the fascia which binds the adrenal to the sheath of the vena cava. The main vein can be seen clearly passing over the front of the medial part of the gland to reach the vena cava (Fig. 3). This vein is not so well seen when the operation is done from behind. When this vein is ligated, the gland can be easily separated from the vena cava and the separation is continued upwards. A long tongue of tissue usually extends upwards behind the right edge of the vena cava, but after division of the main vein, and retraction of the right edge of the vena cava, it is usually possible to surround it gradually by successive pairs of forceps. Only after the medial and lateral borders of the gland, and the upper pole, have been freed, is dissection of the lower surface of the gland completed, between adrenal and kidney. The attachment of the adrenal to the perirenal fascia here maintains that convenient low position of the adrenal which has usually been obtained initially by depression of the kidney. The only danger of the operation on this side is the risk of venous haemorrhage when the dissection is being carried round the extreme upper pole. An ordinary sponge-holding forceps makes a suitably gentle holder for the adrenal gland during dissection.

MALE PSEUDOHERMAPHRODITISM: A HITHERTO UNDESCRIBED FORM

BY

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Of recent years considerable progress has been made in the clinical differentiation of intersexuality, and a now well-recognized form of male pseudohermaphroditism has emerged. Schneider *et al.* (1952) laid down the following criteria for the diagnosis of this type, referred to as "intersex males with purely feminine external genitalia and bodily habitus" by Williams (1952): feminine habitus, primary amenorrhoea, absence or almost complete absence of axillary and pubic hair, blind vaginal pouch with absent cervix, and intra-abdominal testes. They could find only 12 cases in the literature which fulfilled their criteria, and reported six cases of their own. Two further cases have been reported by Beatty *et al.* (1953) and by Armstrong (1953, 1955).

With the introduction of relatively simple techniques for the determination of chromosomal—that is, genetic—sex, first by the skin biopsy method (Moore *et al.*, 1953) and more recently by the even simpler polymorphonuclear leucocyte method (Davidson and Robertson Smith, 1954), a new and potent tool has become available for the elucidation of problems of intersexuality. Already it has been demonstrated that many examples of so-called Turner's syndrome (ovarian—or, better, gonadal—agenesis) are of male chromosomal sex though outwardly of female appearance (Polani *et al.*, 1954; Wilkins *et al.*, 1954; Russell *et al.*, 1955). The application of these techniques to two patients presenting with primary amenorrhoea led to their diagnosis as male pseudohermaphrodites, of a type apparently undescribed in the literature, and which forms the subject of the following report.

Case 1

This patient, aged 19, was referred on account of primary amenorrhoea. The mother and father are normal, and there is a normal sister, aged 16½, whose menarche occurred at about 15 and whose menstruation has remained regular. The patient is about 6 in. (15 cm.) taller than her sister, a little taller than her mother, and the same height as her father. She was of normal height until 11 or 12, when she began to grow rapidly, and is now one of the tallest in the family, which includes no other known examples of sexual abnormality. She has always been thin. The past history included chicken-pox and measles in childhood but no other significant illnesses. The social history was quite uneventful. The patient works as a typist and is happy in her occupation.

Her interests are entirely feminine and appropriate to her age, though socially she is rather retiring, has no boy friends, and does not dance.

On physical examination (Fig. 1) her height was found to be 69 in. (175 cm.), span 71 in. (180 cm.), lower measurement 36 in. (91 cm.), and upper measurement 33 in. (84 cm.); these are definitely eunuchoid proportions. Her weight was 116 lb. (52.6 kg.) and her leanness was quite noticeable. Her voice was that of a girl. The breasts were undeveloped, the nipples and areolae small. The scalp hair was normal and there was a little hair on the upper lip. Hair was present in moderate amount in the axillae and more extensively on the pubis. There was also some hair on the arms and legs. The skin and musculature were normal. The pulse was 80 a minute and the blood pressure 130/80. There was nothing remarkable in the chest or abdomen and there were no inguinal herniae. The external genitalia were of female type, apparently normal except for marked enlargement of the clitoris (Fig. 2), and the labia minora were prominent. A vaginal smear was markedly hypo-oestrogenic.

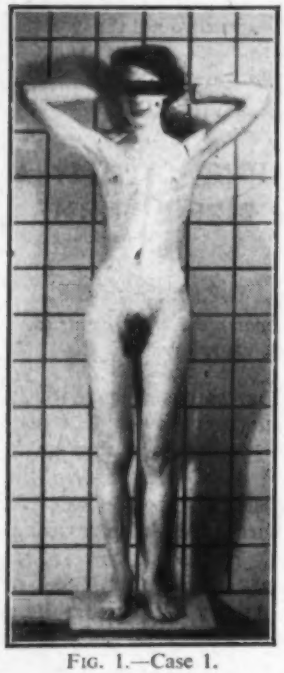

FIG. 1.—Case 1.

The physical findings suggested adrenal hyperplasia producing female pseudohermaphroditism, and she was admitted to hospital for further investigation. Examination under anaesthesia showed the clitoris to measure 4.5 by 1.25 cm. The hymen was small and intact, the vagina about normal in size but with poorly developed rugae. A normal cervix was present, but the uterus was extremely small — about 1 in. (2.5 cm.) long. No adnexa could be felt. A skin biopsy was taken from the medial aspects of the thigh.

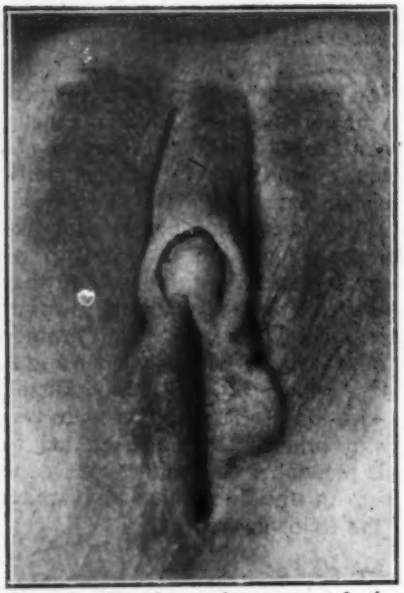

FIG. 2.—Showing enlargement of the clitoris in Case 1.

Laboratory Investigations.—Haemoglobin, 95%; leucocytes, 6,100 per c.mm. (neutrophils 56.5%, lymphocytes 37%, monocytes 5%, eosinophils 1.5%, basophils 0%). Plasma sodium, 146.5 mEq/l.; potassium, 4.7 mEq/l. Urinary neutral 17-ketosteroids, 6.6 mg./24 hours. Urinary oestrogens: oestrone 5.3, oestradiol nil, oestriol 40 µg./24 hours. Urinary gonadotrophins (kaolin adsorption and mouse uterine weight method): nearly 20 mouse units/24 hours. Blood film for genetic sex, male (confirmed by Dr. W. M. Davidson).

Since January, 1955, the patient has had two courses of stilboestrol, each of 20 days. At first the daily dose was 1 mg. and subsequently it was 2 mg. An interval of ten days was allowed to elapse between each 20-day course of tablets. So far (May, 1955) there have been no oestrogen withdrawal bleedings, but a little mammary enlargement has occurred.

Case 2

This patient, aged 24, was also referred on account of primary amenorrhoea. When aged 17 she was seen by a gynaecologist, who stated that the ovaries had not developed and that she would never menstruate. She has four sisters, all older than herself, and all with normal menstruation; three are married with children. There are also a married brother with children, and an unmarried brother. She had measles, mumps, and a tonsillectomy in childhood; apart from these, her past medical history is unimportant. She has a normal feminine outlook and libido, and she works as a machine operator.

FIG. 3.—Case 2. After three months of oestrogen therapy. The pubic hair had been shaved for the previous examination under anaesthesia and some regrowth had occurred.

Her general appearance was that of a tall, eunuchoidal female. Her height was 70½ in. (179 cm.), span 75 in. (190 cm.), upper measurement 34 in. (86 cm.), lower measurement 36½ in. (93 cm.), weight 149 lb. (67.6 kg.). Her voice was noticeably deep. Her breasts were poorly developed, containing a small amount of mammary tissue. The skin was normal, except for the presence of a few pigmented moles and a spider telangiectasis on the neck. The scalp hair was normal; axillary and pubic hair was present, though rather scanty. The musculature was normal, as were the pulse (76 a minute) and blood pressure (120/70). There was nothing remarkable in the chest or abdomen, and there were no inguinal herniae. The external genitalia were of female type and apparently normal, with no enlargement of the clitoris. The vagina was of normal length, but a vaginal smear was markedly hypo-oestrogenic.

She was admitted to hospital for investigation. Examination under anaesthesia confirmed the normality of the vulva, clitoris, and vagina, except for the poor rugose development of the latter. The cervix was small, but not minute; the uterus was rudimentary, not exceeding 1 in. (2.5 cm.) in length. No adnexa could be felt. A skin biopsy was taken from the medial aspect of the thigh.

Laboratory Investigations.—Haemoglobin, 96%; leucocytes, 6,600 per c.mm. (neutrophils 46%, lymphocytes 40%, monocytes 11.5%, eosinophils 2%, basophils 0.5%). Plasma cholesterol, 153 mg. per 100 ml. B.M.R., −5.5 and −6.5%. Urinary neutral 17-ketosteroids, 8.3 mg./24 hours. Urinary oestrogens: oestrone 4.2, oestradiol 2.8, oestriol 17 µg./24 hours. Urinary gonadotrophins, less than 5 mouse units /24 hours. Blood film for genetic sex, male (confirmed by Dr. W. M. Davidson). *X*-ray films of the pelvis revealed a masculine configuration, and the radiological bone age was estimated as 18–20 years—that is, 4 to 6 years retarded.

Since February, 1955, she has been taking ethinyloestradiol, 0.1 mg. daily, in 20-day courses, with 10 days between each course. A scanty oestrogen withdrawal bleeding followed the second course, and some enlargement of the breasts has occurred. Fig. 3 shows the patient after three months of treatment.

Discussion

First, it is pertinent to point out that it has been found easier to reach a decision regarding the chromosomal sex from a study of leucocytes in blood films than from skin biopsies, though the findings in the latter have been consistent with the conclusions reached from blood-film studies. Because these conclusions were so surprising, blood films were sent to Dr. W. M. Davidson, who very kindly reported on them, *without having been informed of the clinical features of the patients.* His interpretation, which confirmed my own, was thus completely unbiased, and, since there have so far been no reports of erroneous results from the method of chromosomal sex determination, it seems justifiable to regard these two patients as of male genetic sex.

The possibility that Case 1 was an example of adrenal hyperplasia causing female pseudohermaphroditism was ruled out by the finding of a normal 17-ketosteroid excretion, and the true state of affairs was revealed by the blood film.

The patients had the following features in common: they presented as "females" complaining of primary amenorrhoea; they were tall, with eunuchoidal proportions; there was little or no mammary development, and pubic and axillary hair was present in essentially normal amounts; the vagina was of normal length, though with evidence from the mucosa of marked oestrogen deficiency; the cervix was almost normal but the uterus was very small; no adnexa could be palpated; the 17-ketosteroids were in the normal range and the urinary oestrogens definitely higher than usually found in primary amenorrhoea; the chromosomal sex was male. The only important differences between the patients were the presence of a definitely enlarged clitoris in one, who also had a significant (normal) output of urinary gonadotrophins, and of a rather deep voice in the other. It would, of course, have been of great interest to determine the histological status of the gonads, but it was felt that laparotomy could not be justified solely on the grounds of scientific curiosity.

The differentiation of this type of male pseudohermaphroditism from the more generally recognized form of "intersex males with purely feminine external genitalia and bodily habitus" depends upon the presence of body hair and normal vagina and cervix in the former and their deficiency in the latter, together with the deficiency of mammary development in the former and its relative normality in the latter. It is also of interest that whereas in the two cases described here the oestrogen excretion was not unlike that found in normal females, while the vaginal smears appeared to be very hypo-oestrogenic, in the male pseudohermaphrodites reported by Beatty *et al.* (1953) and by Armstrong (1955) the oestrogens were oestrone 1.5, oestradiol 2.5, oestriol 2.0 μg./24 hours for the former (whose vaginal smear showed definite evidence of oestrogenic stimulation) and oestrone 2.44 and 3.1, oestradiol 0.5 and 1.4, and oestriol 2.0 and 1.6 μg./24 hours for the latter. It is tempting to postulate an enhanced tissue responsiveness to oestrogens in the "classical" male pseudohermaphrodite and a decreased responsiveness in the patients reported here, though it must be admitted that one, at any rate, has shown sufficient endometrial responsiveness to have oestrogen withdrawal bleedings.

The other conditions from which this new type of male pseudohermaphroditism should be differentiated are the gonadal agenesis syndrome ("Turner's syndrome") and primary and secondary female hypogonadism. In the gonadal agenesis syndrome the patient is short and stocky, often showing various congenital anomalies such as webbed neck, cubitus valgus, coarctation of the aorta, squints, polydactyly, and so forth; there is no mammary development, and body hair is scanty or absent; the vagina and uterus are infantile; the urinary gonadotrophins are usually high and the oestrogen excretion is low; and the chromosomal sex may be male or female. In primary (excluding the above) and secondary hypogonadism the chromosomal sex is female; mammary development is absent and the genitalia are infantile; the height may be increased in primary, and normal, increased, or decreased in secondary hypogonadism; body hair is scanty or absent; the urinary gonadotrophins are increased in primary and decreased in secondary hypogonadism, while the oestrogen excretion is low in both. These differential features are summarized in the Table.

Thus, apart from the clinical features, these various causes of primary amenorrhoea require for their differentiation chromosomal sex determination (by leucocyte or skin biopsy techniques) and urinary gonadotrophin estimation. Determination of the oestrogen excretion is helpful but not necessary; examination of the vaginal smear is also helpful, and is much easier to carry out.

With the new type of male pseudohermaphroditism reported in this paper, it would seem that there are at least three forms of "intersex male with purely feminine external genitalia and bodily habitus"—that is, in addition to this new type, the "classical" type and the gonadal agenesis syndrome. A logical interpretation of the intersexualizing process is available for the last type: the experimental work of Jost (1947) and of Raynaud and Frilley (1947) has shown that removal or the destruction of the gonads of embryos in mice and rabbits in the sexually indeterminate stage leads to the development of foetuses all of which are apparently female, the males having undergone intersexualization; it seems probable that a failure of migration of the primordial germ cells, the sex of which is already determined genetically, from the yolk sac endoderm to the cortex of the genital ridge would result in failure of differentiation of the cortical elements of the gonad (which evidently have an endocrine influence in the normal male embryo) and so lead to the same intersexualization as that demonstrated experimentally by Jost and by Raynaud and Frilley.

This interpretation cannot apply to the "classical" type of male pseudohermaphrodite, in which the gonads appear to be intact and are indistinguishable from undescended testicles found in otherwise normal males. The evidence suggests that the abnormality in these patients consists in an increased tissue sensitivity to oestrogens; the existence of such a state in the sexually undifferentiated embryo would then lead to

Differential Diagnosis of Primary Amenorrhoea (excluding imperforate hymen, uterine agenesis, and other purely anatomical causes)

	Stature	Congenital Anomalies	Breasts	Body Hair	Vagina	Cervix	Chromosomal Sex	Gonadotrophins	Oestrogens
"Classical" male pseudohermaphroditism	Normal or tall	—	Developed	Absent or very scanty	Short, oestrogenized at least in some	Minute or absent	Male	Normal	Low
New type of male pseudohermaphroditism	" " "	—	Little or no development	Within normal limits	Normal, unoestrogenized	Normal	"	"	Apparently normal
Gonadal agenesis syndrome	Short	Frequent	Undeveloped	Absent or scanty	Infantile	Infantile	Male or female	High	Low
Primary female hypogonadism	Tall	—	"	" "	"	"	Female	"	"
Secondary female hypogonadism	Tall, normal, or short	—	"	" "	"	"	"	Low	"

the same form of intersexualization as described above. Since a familial tendency to this type of male pseudohermaphroditism has been reported (Schneider *et al.*, 1952) one may suppose that the postulated oestrogen hypersensitivity is genetically determined. This explanation will not suffice for the new type, where the oestrogen levels seem to be higher and yet there is little or no mammary development and the vaginal smear appears to be hypo-oestrogenic. In the absence of factual knowledge of the gonadal structure in these patients it is probably better to refrain from speculation on the mechanism of intersexualization.

Summary

Two examples of a new and apparently undescribed type of male pseudohermaphroditism are reported. Both patients presented as eunuchoidal "females" complaining of primary amenorrhoea. They had normal axillary and pubic hair, little or no mammary development, and normal external genitalia, except for marked enlargement of the clitoris in one. The cervix was about normal, but the uterus was rudimentary and the vaginal smear was markedly hypo-oestrogenic. The urinary 17-ketosteroids were normal, and the oestrogen levels seemed to be definitely higher than those found in other cases of primary amenorrhoea. The gonadotrophins were low in one and normal in the other. The chromosomal sex, as determined by blood-film studies, and confirmed by skin biopsies, was male.

The differentiation of this type of male pseudohermaphroditism from the generally recognized variety of "intersex male with purely feminine external genitalia and bodily habitus" and from other relevant forms of hypogonadism is discussed.

I am indebted to Dr. W. M. Davidson for examining and reporting on the blood films, and to Dr. Sylvia Dawkins, who referred Case 1, and Dr. E. E. Pochin, who referred Case 2, for permission to include these cases in the report.

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ADDENDUM.—Since this paper was written R. B. Greenblatt and N. Carmona (*J. clin. Endocr.*, 1955, **15**, 877) have described the case of a 25-year-old tall "female" of eunuchoidal appearance with primary amenorrhoea, failure of breast development, infantile uterus, scanty pubic hair, and markedly enlarged clitoris. The chromosomal sex was male, the vaginal smear was atrophic, the urinary 17-ketosteroids were decreased, and the gonadotrophins were within normal limits. This case resembles very closely Case 1 described above. Laparotomy revealed rudimentary gonads, histological examination of which showed a cortex composed of stroma without follicles and a medulla and hilus containing many "Leydig cells."

The Haemophilia Society, whose president is Sir LIONEL WHITBY, has produced a pamphlet describing its purposes. *The Haemophilia Society: What it is and How it can Help* may be obtained from the hon. secretary, 94, Southwark Bridge Road, London, S.E.1. The society's aims include the provision of fellowship, advice, and help for the individual haemophilic and promotion of the study of the disease. Membership is open to all haemophilics, their families, and friends. The minimum subscription is 5s. a year.

EUNUCHOIDISM IN IDENTICAL TWINS
WITH CONGENITAL FUSION OF THE THORACIC VERTEBRAE

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The occurrence of congenital developmental abnormalities in twins, uniovular or binovular, is not unusual, and numerous instances have been reported in the literature. The abnormality may be single, or multiple abnormalities may coexist, and any of the systems may be involved. Endocrine disturbances may occur, and infantilism and pituitary dwarfism in identical male twins have been reported by van Braam Houckgeest and Sanders (1940) and Guillain and Rouzaud (1943), in the latter instance accompanied by retardation of intellectual development and the presence of major epilepsy in one of the twins. A careful search of the literature, however, has not disclosed any report of eunuchoidism in identical twins, and the following is therefore of interest.

Case 1

A dustman aged 40 complained of having had painless swelling of the feet and ankles for a fortnight. There was obvious endocrine disturbance, and he was admitted to hospital for further investigation.

He was one of twin brothers. He had always been of large physique, and the brothers were the biggest pupils in their class at school, but were poor scholars and did not reach a high standard before leaving school at the age of 14. He had never shaved. He was unmarried, and had shown no interest in the female sex, but admitted to masturbating about twice monthly with ejaculation, although spontaneous nocturnal emissions had not occurred. He said he drank 12 pints (6.8 litres) of fluid a day and passed large quantities of urine. Tibial osteotomy for genu valgum had been performed when he was aged 16.

On examination he was found to be mentally backward, of placid temperament, very lethargic, unruffled, and easy to please, and was indifferent to his physical condition apart from the recent ankle oedema. He looked younger than his years, and the voice was high-pitched and unbroken. The skin of the face was smooth and devoid of hair, and the axillary and pubic hair was sparse, the latter being of female distribution. There was considerable obesity, the fat being of "buffalo" distribution, with gynaecomastia and colourless striae of the abdomen. The limbs were excessively long and genu valgum was present, but his height was diminished by a gross dorsal kyphosis. The genitalia were of infantile proportions, and the testes, the size of small beans, were fully descended into the scrotum (Fig. 1). The prostate could not be felt on rectal examination.

Examination of the systems revealed no gross abnormality. The heart sounds were normal and the blood pressure was 160/100. There was no optic atrophy and the visual fields were full. Pitting oedema was present over the lower third of both legs.

The following investigations were carried out: haemoglobin, 92% (13.6 g.%); Wassermann reaction negative; blood urea, 24 mg. per 100 ml. Urinalysis: albumin present; pus cells present in moderate numbers; red cells present in large numbers; casts absent; moderate numbers of calcium oxalate crystals seen; culture, no growth obtained. Serum

calcium, 10 mg. per 100 ml.; blood cholesterol, 160 mg. per 100 ml. B.M.R.—14% (normal). Fasting blood sugar, 86 mg. per 100 ml. Blood sugar after ingestion of 50 g. of glucose: ½ hour, 166 mg.; 1 hour, 114 mg.; 1½ hours, 100 mg.; 2 hours, 64 mg. per 100 ml. Urine was free from sugar throughout. E.C.G. was normal. Urinary excretion of 17-ketosteroids, 7.2 mg. in 24 hours. Blood group A_1 Rh positive (see Table I for detailed analysis).

The maximum fluid intake never exceeded 70 fl. oz. (1,980 ml.) in 24 hours, when the output was 90 fl. oz. (2,550 ml.). A seminal specimen could not be obtained, and biopsy of the breast or testis was not performed.

TABLE I.—*Blood Grouping*

Case	ABO	Rh	MN	S	P	Lu	Kell	Le^a	Le^b	Fy^a
1	A_1	R_1r (CDe/cde)	M	+	++	−	−	−	−	−
2	A_1	R_1r (CDe/cde)	M	+	++	−	−	−	−	−

TABLE II.—*Anthropometrical Data*

	Case 1	Case 2
Weight	238¼ lb. (108·2 kg.)	225 lb. (102 kg.)
Height	66⅓ in. (168·2 cm.)	67½ in. (171·4 cm.)
Span	71½ in. (181 cm.)	73 in. (185·4 cm.)
Vertex to pubis	31 in. (78·7 cm.)	32½ in. (82·5 cm.)
Pubis to ground	35 in. (88·9 cm.)	35 in. (88·9 cm.)

Radiography of the skull showed no bone change or evidence of intracranial calcification. The pelvis was large and flattened. The femora were rather massive and the epiphyses had united normally. No abnormality was shown in the hands, apart from increased length of the metacarpals and phalanges. Multiple calculi were present in the left kidney. The report on the vertebral column states: "Well-marked dorsi-lumbar kyphoscoliosis. There is fusion of the bodies in the mid-dorsal region anteriorly—this is obviously congenital. Osteoarthritic changes also present in the lower dorsal region" (Fig. 2). The anthropometrical data are shown in Table II.

Case 2

The twin brother of Case 1 was then seen: the striking similarity in appearance and bodily configuration is shown

FIG. 2.—Case 1. Radiograph of dorsal spine.

FIG. 4.—Case 2. Radiograph of dorsal spine.

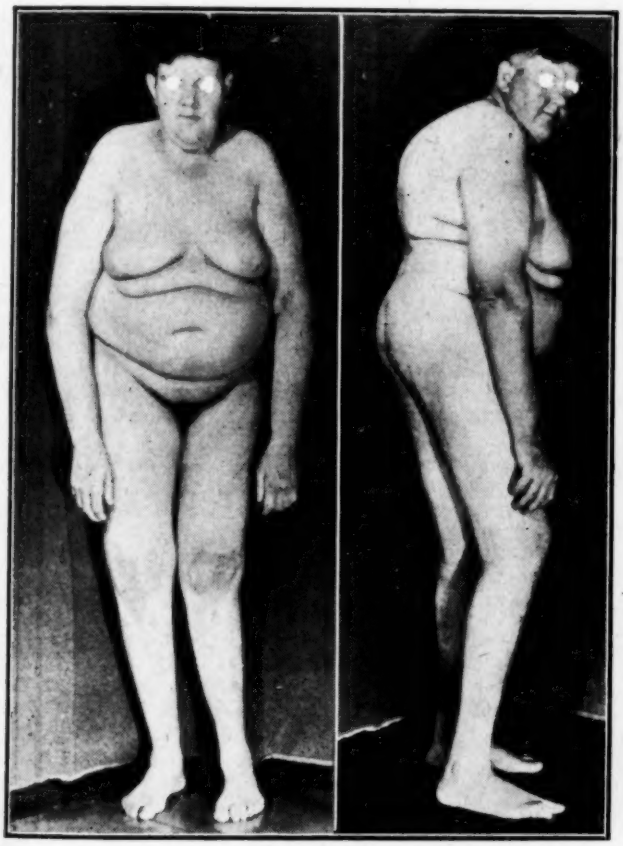

FIG. 1.—Case 1.

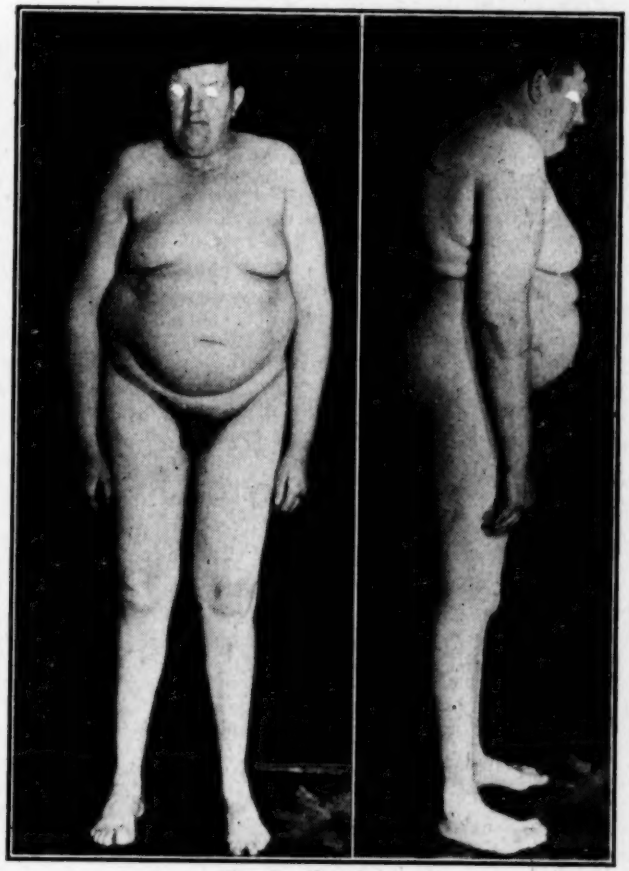

FIG. 3.—Case 2.

in Fig. 3. Obesity of the pituitary type was present with gynaecomastia, and there was genu valgum and considerable dorsal kyphosis, though less severe than in the brother. The genitalia were infantile and a left inguinal hernia was present in the scrotum. He did not shave, was unmarried, and displayed no interest in the opposite sex. He, too, was employed as a dustman, and his temperament and mental development closely resembled those of his brother.

Radiography of the dorsal spine showed the same congenital abnormality to be present (Fig. 4). There were no opaque renal calculi.

His blood group was A_1, Rh positive, and is identical with that of his brother (Table I). No other investigations were carried out. The anthropometrical data are seen in Table II.

Family History

The twins are the youngest of a family of 12 children, comprising five males and seven females, and were born when their mother was aged 46. The eldest son had been killed while serving in the first world war, and, so far as could be ascertained, was physically and mentally normal. The remaining two brothers had died, one from meningitis in childhood and the other from convulsions in infancy, and no further medical details are available of them. A sister had died of pneumonia in childhood and another had died in childbirth. The five remaining sisters are healthy and married, with families of from three to six children, of both sexes. They are thus quite fertile. When interviewed they appeared to be of normal intelligence, and each asserted that the twins had always been of a different mental and physical development from the rest of the family. The mother stated that the twins had been abnormal since birth, and the family practitioner had, in fact, told her that they "shared the brains of one." She confirmed that they had fared badly at school, and had been of large physique even in their youth.

The mother and daughters were unaware of any abnormalities resembling the present among cousins, uncles, or any of the 23 grandchildren, and the abnormalities therefore appear to have arisen sporadically rather than have been inherited as a familial trait.

Discussion

In their study of organic nervous disease in identical twins Kinnier Wilson and Wolfsohn (1929) declared "the extreme similarity of certain human twins to each other is strongly in favour of their uniovular origin," and quoted Abt (1924) that "homologous twins usually show marked similarity physically as well as mentally. Not rarely they show the same anomalies and faults of development." They concluded, *inter alia*, that (1) in health homologous twins show a striking similarity of structural, functional, and mental equipment; (2) when anomalies and deformities are present in identical twins they are most probably the result of inherent defects and are always present in both twins; (3) an anomaly of development is always similar and equivalent in both homologous twins; and (4) biologically considered, homologous twins are only one individual; physically they are two (this last is of interest in view of the comment of the family practitioner to the mother).

Among the reasons advanced by Guillain and Rouzaud (1943) for assuming their twins to be monozygous were their resemblance, the same disturbance in general development and the same abnormalities present in the brothers, and the similarity in their blood group. In view of these statements there can be no doubt that the patients here presented are identical or uniovular twins. They are of the same sex, and the striking similarity in facial appearance and body configuration is obvious from the accompanying photographs. The same skeletal deformity is present in both, and both exhibit gynaecomastia and infantile genitalia. They are also of the same blood group. The colour of their eyes is the same, as is also the shape of their ears and hands. Their hair is similar in colour and texture, and the hair pattern is the same, the whorl turning in the same direction (so that they are not mirror images of one another). Thus the criteria for the recognition of identical twins formulated by van Braam Houckgeest and Sanders (1940) are also fulfilled. They are not colour-blind (Ishihara method) and do not suffer from anosmia. Their temperaments are similar and both are intellectually retarded. They share the same interests or lack of interests, and are both employed as dustmen, and even work on the same dustcart. Their fingerprints are not identical, but it is known that this is not found in identical twins. We feel justified in concluding that our patients are identical twins.

The nature of the endocrine disturbance presents a difficult problem. In eunuchoidism the primary defect is in the gonads and not in the pituitary. In infantilism the defect is in the pituitary, and the patient is usually thin and subnormal in stature, as the secretion of pituitary growth hormone is also defective. In the two brothers with gynaecomastia reported by Ferriman (1954) there were some features suggestive of eunuchoidism, but the dwarfism and low output of urinary gonadotrophins indicated that their testicular hypoplasia was secondary to a pituitary defect. The differentiation from Fröhlich's syndrome is more difficult, but in this condition the patient is usually subnormal in height and the syndrome is due to a lesion affecting the pituitary-hypothalamic mechanism, which may itself give rise to symptoms, although it does not invariably do so. ("Fröhlich's syndrome" is often loosely applied to a condition Simpson (1948) has renamed "adipose gynandrism," and, clearly, our patients were not suffering from this.)

The presence of diabetes insipidus, at first suspected, was not confirmed, and the excretion of 17-ketosteroids suggests that the pituitary is intact. An estimation of the gonadotrophic hormone in the serum and urine would have been valuable, as this is normal or above normal in eunuchoidism and deficient or absent in pituitary deficiency or Fröhlich's syndrome. Unfortunately, we were unable to do this. Eunuchs, though usually tall, may be of average height. The height of our patients, though average, would have been greater but for the extent of the kyphosis. The span of their outstretched arms is greater than their height, the pubis-to-ground measurement is greater than the pubis to vertex, and the excretion of 17-ketosteroids in Case 1 is on the low level of normal. All these features are in keeping with a diagnosis of eunuchoidism. Their sexual behaviour and outlook, their mentality and passive and accommodating demeanour, also point to this diagnosis.

The nature of the breast changes is worthy of comment. There was no enlargement of the areola or nipple, and the appearance of the breasts suggested a local disposition of fat comparable to the excess of fat elsewhere. In the youth with gynaecomastia and testicular atrophy described by Ferriman (1950) enlargement of the areola and nipple was present, and biopsy of the breast showed hyperplasia of the duct elements and fibrous tissue. He discussed the mechanism whereby gynaecomastia may appear with aplasia of the testes. As no breast biopsy was performed on our patients we are unable to confirm that the breast enlargement is simply due to a local acquisition of fat, or whether hyperplastic changes are present, but, clinically, we believe the former to be the more likely.

The aetiology of the condition is open to speculation. Eunuchoidism is due to a primary defect of the gonads which may follow an infection, such as mumps, or result from trauma or interference with the blood supply to the testes; but the commonest cause of eunuchoidism appears to be genetic (Simpson, 1948). Ferriman (1950) expressed the opinion of Dr. Raymond Greene, that the testicular aplasia was very likely due to a genetic disturbance, though in his later report he thought the dwarfism and low secretion

of gonadotrophin pointed to a pituitary origin for the testicular hypoplasia. In the cases under review, not only has the eunuchoidism to be accounted for, but also the identical skeletal deformity and the mental retardation, which is uncommon in eunuchs, who are usually of normal or above normal intelligence. The three abnormalities may be explained on a single basis if the concept of a degeneration of unknown aetiology in the parental germ plasm is accepted. If the cause of the defect be a matter of heredity in the germ cells, the monovular twins should be alike—either both normal or both defective (Macklin, 1936). It is probably significant that the twins were the last of 11 pregnancies, and at the time of their birth the ages of the father and mother were 44 and 46 years respectively.

The absence of colour-blindness and anosmia from our patients strengthens the belief that the condition has arisen sporadically, as Kallman *et al.* (1944) concluded that these tended to be associated with eunuchoidism only when hypogonadism appeared as a familial trait.

Summary

Eunuchoidism in identical twins is described, together with mental retardation and congenital fusion of the thoracic vertebrae.

Reasons are advanced for the belief that the twins are uniovular and that the condition has arisen sporadically, and the opinion is also expressed that the primary cause for the abnormalities lies in an unknown degeneration of the parental germ plasm.

Our thanks are due to Dr. D. Lehane, Director of the Regional Blood Transfusion Centre, and Mr. W. Donohoe, senior technician, for the investigation and report on the blood groups.

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The National Old People's Welfare Committee, now to be called the National Old People's Welfare Council, "is now established as the accepted focus and centre to deal with the diverse and often difficult problems relating to the welfare of old people," said Mr. HAROLD MACMILLAN last year when he was Minister of Housing and Local Government. The *Progress Report* for 1954 shows that, while the main work of the council in co-ordinating the efforts of both voluntary and government bodies working for old people has continued satisfactorily, other schemes have also advanced. Training courses for voluntary and paid workers, including one for matrons of homes, have been developed. In Birmingham alone 310 voluntary visitors visited 1,735 old people regularly. The King George VI Foundation gift of £80,000 has been used to build new clubs or improve those existing. By September, 1954, 5,000 social clubs for the elderly were reported to exist. A building society has opened a home for the mentally frail in London, and many accommodation problems have been dealt with; interest in boarding-out old people as pioneered in Plymouth and Exeter in 1952 has revived. The council has sponsored several publications to educate the public on the problems of the elderly and how they can best be tackled.

PROLONGED PREGNANCY

BY

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A prolonged pregnancy may be defined as a pregnancy which continues for more than 14 days after the expected date of confinement provided that the estimation of this date is accurate. It occurs with relative frequency in lower animals, and most obstetricians would agree that it also occurs in human species. Many authentic cases have been published, and as examples the cases of Hendry (1921), Wells (1948), and Smith (1951) may be mentioned.

By definition the diagnosis depends upon an accurate estimate of the expected date of confinement. This is obtained by calculation based on Naegele's rule, and the fallacies of this calculation are such that it is difficult to decide in any given case whether pregnancy is really prolonged or whether the calculation is in error. The intelligence of the patient, her accuracy of observation, and the regularity of her menstrual cycle all help in reaching a decision. The size of the uterus in early pregnancy and the date of quickening are also useful aids. In retrospect the weight of the baby at birth may be used as a check on the accuracy of diagnosis. An investigation was undertaken, utilizing these aids to diagnosis, in order to discover the incidence of prolonged pregnancy and the pathological significance of the condition.

The Investigation

A clinical investigation is more satisfactory if all cases are supervised personally, but an investigation into prolonged pregnancy requires such a large series that personal supervision is impossible. Most published reports deal with cases which have been collected from hospital records, a method which has obvious disadvantages. In an attempt to overcome these disadvantages an investigation based on personal interview was undertaken. Approximately 6,000 women were interviewed by me during 1953 and the early part of 1954. These women were patients in the Jubilee Maternity Hospital or the Royal Maternity Hospital, Belfast, and the interviews took place during the first week of the puerperium. The series was consecutive, excluding holidays, and the interviews were continued until 5,000 case records had been obtained.

It will be noted that approximately one in six cases were excluded from the series, but it must be emphasized that these exclusions were made before the fate of the child had been ascertained. The reasons for exclusion were: (1) A fabrication of the "dates" to agree with a marriage early in pregnancy. (2) An uncertain estimate of the date of confinement due to (*a*) pregnancy commencing during lactation, or (*b*) prolonged or irregular menstrual cycles, or (*c*) lack of ordinary intelligence on the part of the patient.

If the duration of pregnancy is being investigated an interview during the first week of the puerperium has many advantages. Firstly, the patient retains a clear knowledge of the date of her last menstrual period, the date of quickening, and her menstrual history prior to pregnancy. Secondly, her case records are available to furnish information about the size of the uterus at various stages in pregnancy. Lastly, the date of confinement, the weight of the child, and the outcome are known. Information which has been obtained in this way may be criticized on the grounds that, as delivery has occurred, the patient may tell her story accordingly. It

was felt, however, that patients were not influenced by their knowledge of the date of confinement, and as the fate of the child was the last question at each interview the results were not affected by any desire to accentuate or minimize the lethal effects of prolonged pregnancy.

Average Duration of Pregnancy

There were 4,389 patients who started spontaneously in labour with single vertex presentations. In each case the estimated date of confinement was calculated by Naegele's rule, and the accuracy of this date was checked by as many means as the patient and her clinical notes could provide. The actual date of confinement was compared with this estimated date and the discrepancy was calculated. A graph (Fig. 1) was prepared to illustrate the results—this deals with

FIG. 1.—Onset of labour in 3,989 cases in which labour started within three weeks of E.D.D.

3,989 patients who started in labour within three weeks of the estimated date of confinement. Fig. 1 shows that there was a gradual increase in the number of confinements as the estimated date approached, and the peak persisted for approximately seven days thereafter.

The findings suggest that the common practice of calculating the expected date from the last rather than the first day of the menstrual period has something to commend it: a considerable number of patients thus escape the mental anxiety and the rigours of castor oil which so often accompany the 41st week of pregnancy.

The age and parity of patients in this series had no influence on the time of onset of labour, thus confirming the views of Hotelling and Hotelling (1932) and Gibson and McKeown (1950).

Fig. 1 corresponds very closely with the graph of Speitkamp (1937), who investigated 14,078 hospital cases. This similarity was a disappointment to me, as it suggests that my personal approach added nothing to the accuracy obtained by a perusal of hospital records.

The results are considered on a percentage basis in Table I. It will be seen that 53.1% of patients were delivered

TABLE I.—*Onset of Labour*

	Days Before E.D.D.				E.D.D.	Days After E.D.D.				Total No.
	22+	21–15	14–8	7–1		1–7	8–14	15–21	22+	
No. of cases	323	207	490	977	176	1,179	714	246	77	4,389
% ..	7·3	4·7	11·2	22·2	4	26·9	16·3	5·6	1·8	—
					53·1			7·4		
Breech % ..	21·6	1·5	10·9	21	5	20·3	15·2	1·5	3	138
Twins % ..	40·1	9·9	10·9	13	1·1	16·3	5·4	2·2	1·1	92

in the 40th or 41st weeks, a figure which corresponds closely with the 49.5% reported by McKiddie (1949). Prolonged pregnancy occurred in 7.4%, and this corresponds almost exactly with the findings of Clayton (1941) and Rathbun (1943). Pregnancy was prolonged for more than three weeks in 1.8%, as compared with 0.65% (Fruhinsholz and Richon 1940) and 3.8% (Burger and Korompai, 1939). Kortenoever (1950) reports a series of 13,000 consecutive deliveries in Holland, with 13.53% of the patients going more than 14 days and 8% more than 20 days beyond the estimated dates of confinement. From experience gained during the present investigation it is felt that such high percentages must result from the inclusion of cases with prolonged menstrual cycles. It is generally accepted that ovulation tends to occur 14 days before the onset of menstruation rather than 14 days after the onset of the previous menses, the event upon which Naegele's calculation depends. If the menstrual cycle is prolonged there is therefore an apparent but not a real increase in the duration of pregnancy, a point emphasized by Reynolds (1938).

In Table I percentages dealing with twin pregnancy and breech presentation have been included. As expected, there is a tendency to premature labour in twin pregnancy, 40.1% being delivered more than 21 days before the estimated date. The same tendency is apparent to a lesser extent with breech presentation, but it is probable that the breech presentation is the result of premature labour rather than the cause of it.

Relationship Between the Menstrual Cycle and the Duration of Pregnancy

All patients supplied details about their menstrual history, and the opportunity was taken to test the contention of Jolly (1928) and Seager (1953) that the duration of pregnancy is related to the length of the menstrual cycle. Knaus (1949) and Bartelmez (1953) have stressed the irregularity of the "regular" menstrual cycle; this irregularity was very apparent in the present series, particularly among patients who stated that they menstruated once a month. Some patients had regular cycles of 26, 27, 29, or 30 days, with diary entries as supporting evidence. Such cases, 245 in number, were utilized in the preparation of Table II pro-

TABLE II.—*Relationship Between Menstrual Cycle and Pregnancy*

Average Cycle (Days)	No. of Cases	Average Week of Onset of Labour	Estimated Week of Onset
26	62	41	41 (286 days = 11 cycles of 26 days)
27	73	40	39 (270 ,, = 10 ,, ,, 27 ,,)
29	54	41	42 (290 ,, = 10 ,, ,, 29 ,,)
30	56	41	39 (270 ,, = 9 ,, ,, 30 ,,)

vided that, in addition, labour began spontaneously within 21 days of the estimated date of confinement. The average week in which confinement occurred was compared with the average calculated on the basis that labour followed a certain number of completed cycles. In this small but accurate group of cases there is no convincing evidence that the length of the menstrual cycle has any influence on the duration of pregnancy.

Foetal Mortality

There were 248 foetal deaths, and in Table III these have been correlated with the week in which they occurred. It will be seen that the foetal mortality is minimal during the 41st and 42nd weeks. There is a double increase in the 43rd week and a triple increase subsequently. This bears out the findings of Gibberd (1952), Clayton (1953), and Walker (1954), and suggests that prolonged pregnancy has a pathological significance justifying the use of the term "post-maturity." It will be noted that in Table III the foetal mortality included neonatal deaths occurring within

TABLE III.—*Foetal Loss*

	Days Before E.D.D.				E.D.D.	Days After E.D.D.				Total
	22+	21–15	14–8	7–1		1–7	8–14	15–21	22+	
Total cases	446	248	563	1,076	195	1,252	757	263	87	4,887
Foetal loss*	119	14	18	33	5	26	15	12	6	248
% lost ..	26·7	5·6	3·2	3·1	2·6	2·1	1·9	4·8	6·9	5·1
									5·1	

* (*a*) The foetal loss includes neonatal deaths within 12 hours of birth. (*b*) Twins are excluded. (*c*) Cases of intrauterine death are included in the week in which death occurred.

12 hours of delivery. As many patients were interviewed on the day after delivery, later neonatal deaths were excluded —indeed, most of the neonatal deaths occurred within a few minutes of delivery, resuscitation having failed to establish respiration.

Smith (1951) has drawn attention to the difficulty of rearing the post-mature infant, and Clifford (1954) supported this view. The latter gave the following reasons for this difficulty: (*a*) a reduction in the quantity of liquor amnii and vernix caseosa leads to cracking of the skin and increases the risk of neonatal infection. (*b*) A reduction in placental efficiency leads to loss of weight, meconium staining, and attempts at intrauterine respiration. The latter causes hyaline membrane formation with a tendency to neonatal atelectasis.

It is possible, therefore, that the foetal loss attributable to post-maturity is greater than that shown in Table III, although, as an obstetrician, I have the impression that the post-mature baby causes no more anxiety than any other baby after respiration has been satisfactorily established.

Death *in utero* is often followed by a considerable interval before labour starts, and this may produce an apparent aggravation of the post-maturity problem. Clifford, Reid, and Worcester (1951) reported a foetal mortality of 11.4% in confinements after the 300th day, but more than half these deaths occurred at unstated intervals before the onset of labour. To avoid this difficulty, intrauterine deaths have been assigned to the week in which they occurred and not to the week of delivery: it is felt that this gives a fairer picture of the post-maturity problem.

Why Does Post-Maturity Give Rise to Foetal Mortality?

It has been suggested by Malpas (1933) that a number of post-mature deaths result from foetal abnormality. However, in this series all abnormal babies had either died *in utero* or been born before the estimated date of confinement.

Ballantyne and Browne (1922), in an exhaustive article, stressed the excessive size of the post-mature foetus. They held that the increased foetal mortality was due to birth trauma, and, in the custom of that time, they advocated induction of labour at term to avoid the dangers of disproportion. Calkins (1948) and Mills (1953) suggested that foetal growth may cease after term, and that, as placental efficiency decreases, the baby may lose weight. Arnot (1942), Wrigley (1946), and McKeown and Gibson (1951) calculated the babies' weights in relation to their maturity, and the results tended to support this view. In the present series the average weights of babies were calculated, the investigation being limited to babies born at weekly intervals before and after the estimated date of confinement. The results are shown in Table IV.

TABLE IV.—*Weight of Babies Born at Weekly Intervals Before and After E.D.D.*

	−21 Days	−14 Days	−7 Days	E.D.D.	+7 Days	+14 Days	+21 Days	All Over +21 Days
No. of cases	33	61	120	195	185	78	20	80
Av. weight in lb. ..	6·3	6·5	6·9	7·4	7·5	8·5	8·3	8·3

There was a steady increase in the average weight weekly until the 42nd week and subsequently a slight drop. No post-mature baby was of excessive size, and, with two exceptions, disproportion was not regarded as a cause of foetal mortality. The exceptions both died as the result of unexpected difficulty in delivery of the shoulders, a risk which Casagrande (1939), Koff and Potter (1939), and Wrigley (1946) have emphasized.

In Table V another attempt has been made to assess the cause of foetal mortality. This table again emphasizes that trauma does not play a significant part in causing post-mature mortality. The majority have no obvious cause—

TABLE V.—*Foetal Loss (including trauma but excluding other obvious causes of death)*

	Days Before E.D.D.				E.D.D.	Days After E.D.D.				Total
	22+	21–15	14–8	7–1		1–7	8–14	15–21	22+	
No. of cases	353	242	554	1,061	194	1,245	754	260	87	4,750
Trauma	5	1	2	7	1	1	2	1	0	20
% lost	1·4	0·4	0·4	0·6	0·5	0·03	0·3	0·38	0	0·4
Doubtful cause	21	7	7	11	3	18	10	8	6	91
% ..	5·9	2·9	1·4	1	1·5	1·5	1·3	3	6·9	1·9

that is, they form a "mysterious" group. Gibberd (1952) and Clayton (1953) refer to this mysterious group and consider that death results from foetal anoxia. Walker (1954) has produced striking experimental evidence to support this view, and his work goes far to establish that the risk of post-maturity is the risk of intrauterine anoxia.

Accepting foetal anoxia as the reason for the foetal mortality associated with post-maturity, it is important to ascertain when the anoxia is likely to appear. In order to obtain information relating to this question a series of 564 stillbirths were investigated. These stillbirths occurred in the Royal Maternity Hospital, Belfast, during the years 1946–53 inclusive, and the details were obtained from hospital records. In Table VI the causes of death are shown. There

TABLE VI.—*Cause of Death in a Series of 564 Stillbirths*

Cause of Death	No. of Cases	Cause of Death	No. of Cases
Abnormal foetus ..	119 (21·1%)	Syphilis ..	7 (1·2%)
Toxaemia of pregnancy	105 (18·6%)	Diabetes ..	5 (0·9%)
Accidental haemorrhage	73 (12·9%)	?Before labour	88 (15·7%)
Prolapse of cord ..	21 (3·7%)	?In labour ..	79 (14·0%)
Placenta praevia ..	14 (2·5%)	?During delivery	53 (9·4%)

were a considerable number of "mysterious" deaths, and these were divided into (*a*) deaths before labour, (*b*) deaths in labour, and (*c*) deaths during delivery. A number of the deaths during delivery were undoubtedly due to trauma. However, the records and even the post-mortem findings were often inconclusive, and it was decided to include all traumatic deaths in the "mysterious" groups.

The cases were divided according to the maturity at the time of foetal death, and four histograms were prepared (Fig. 2). These histograms show the relative frequency of (*a*) death due to obvious causes, (*b*) death before the onset of labour, (*c*) death in labour, and (*d*) death during delivery. The histograms clearly demonstrate that as the maturity increases there is a relative reduction in the obvious causes of foetal death. In addition the risk of intrauterine death before the onset of labour is reduced. The histogram dealing with the post-mature group shows that intrauterine death in labour—that is, during the first and the early second stage—is of prime importance. A considerable proportion of foetal deaths also occur during the actual delivery, the

foetal heart being audible up to that time, or continuing after delivery without the successful establishment of respiration.

The investigation appears to confirm the following points: (*a*) post-maturity is responsible for a definite foetal mortality; (*b*) this mortality results primarily from anoxia *in utero*; and (*c*) the anoxia occurs mainly during the first and second stages of labour.

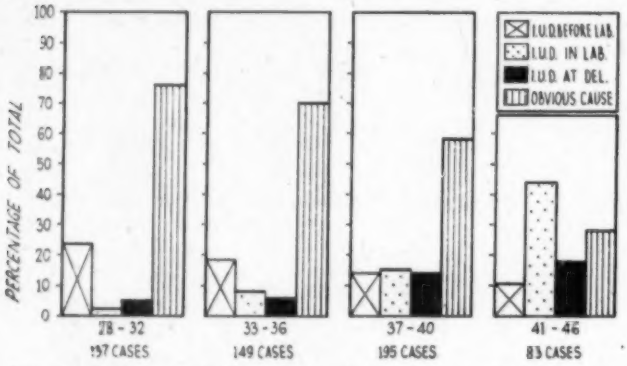

FIG. 2.—Causes of foetal loss in relation to maturity of foetus.

Discussion

The first problem associated with prolonged pregnancy is the diagnosis of the condition, and it is a mistake to consider all pregnancies which continue beyond the estimated date as post-mature. A regular menstrual history prior to pregnancy will underline the accuracy of Naegele's calculation provided that the cycle is not of more than 28 days' duration. The date of quickening may be used as an additional guide if the patient is able to name a definite date. Unfortunately, many patients are unable to remember this date or speak in general terms about feeling life in the fifth month, information which may be influenced by the patient's general knowledge and be of no value. I make a practice of asking all patients, during their first visit, to note the date on which they feel movements and to ensure that this date is incorporated in their clinical notes at their next visit. Thus an accurate date is obtained, and if pregnancy continues for more than five calendar months after this date there is a reasonable presumption that the pregnancy is prolonged. The size of the uterus in early pregnancy may help if a vaginal examination was performed personally and a careful record was made at the time.

In the assessment of a suspected case of prolonged pregnancy the size of the foetus is of value. Weight estimation *in utero* must be approximate, but if the foetus is obviously less than 7 lb. (3.2 kg.) the diagnosis of post-maturity should be revised. Wrigley (1946) noted the rigidity of the post-mature foetus and the diminution in quantity of liquor amnii which gave the impression that the uterus was "full of foetus." I have looked for these signs but have been disappointed in failing to elucidate them to my satisfaction. At one time much was expected of radiography as an accurate guide to maturity, but the size of the foetal skull and the times of appearance of ossification centres are so variable that little help is obtained by such examination.

When it is decided, after careful consideration, that a pregnancy is prolonged the problem of treatment arises. The obstetrician is faced with an anxious patient who is supported by her relatives in demanding action. He is aware of the risk of foetal death *in utero* and knows that, unfair as it may be, the patient will consider him responsible. Thus the stage is set for some form of intervention.

A medicinal induction may be tried, and has the merit of being reasonably safe. However, it causes a physical upheaval of considerable severity for the patient, and if it fails to start labour it aggravates her anxiety. I have formed the opinion that, anyway, a medicinal induction will not be successful unless labour is about to start; if this is true it puts the patient to unnecessary inconvenience. I agree with Browne (1951) that the failure of a medicinal induction does not rule out a diagnosis of post-maturity.

Surgical induction is often employed, and Tennent and Black (1954) reported a series of 633 cases, induced seven days after the expected date, with the commendable foetal mortality of 0.9%. However, there is no method of ascertaining what the mortality associated with masterly inactivity would have been, and Temesvary (1952) found that the foetal mortality was actually increased by induction of labour for post-maturity.

There are certain disadvantages associated with surgical induction. Firstly, the patient may not be post-mature. In the series reported by Tennent and Black (1954) there were 11 babies weighing less than 6 lb. (2.7 kg.), and it is hard to believe that all these were post-mature babies. In the present series only 13 patients had a surgical induction for post-maturity, and one would expect that the diagnosis must have been very definite in these cases. Yet, in retrospect, it was clear that five of the babies were premature. Secondly, earlier in this paper it has been shown that the post-mature baby is mainly at risk in labour, particularly during the first stage. This risk must be increased if most of the liquor amnii has previously drained away, and a previous induction is an unwanted complication if caesarean section has to be performed for foetal distress during labour. Thirdly, there is some risk to the mother following surgical induction. Soon after this series was completed a mother, admittedly in poor general health, was induced surgically because of post-maturity. Labour began about 40 hours later and within six hours mother and baby were dead owing to fulminant sepsis. Because of these dangers and the lack of a clear demonstration of any advantages, I am against induction of labour for post-maturity, and, in particular, deprecate its use as a placebo for the patient.

Having condemned induction of labour, what alternative have I to offer? Firstly, a second opinion about the case is of considerable benefit, and this, of course, applies especially to a patient who intends to have her confinement at home. A vaginal examination is an advantage, and is preferably undertaken in hospital, as at this stage in pregnancy full aseptic precautions are essential. If the head is engaged in the pelvis and the cervix is effaced the patient may be reassured and sent home to await the spontaneous onset of labour. If the head is still free and the cervix is not effaced, I am in favour of stretching the cervix, stripping the membranes from the internal os, and giving a hot vaginal douche. Patients should stay in hospital for 48 hours after this procedure, as there is some risk of infection following an immediate return home.

Secondly, *x*-ray visualization of the foetus is a help. With standard films the picture gives an idea of the foetal size and it excludes some of the abnormalities which could cause foetal distress during labour.

Lastly, the management of labour requires special attention, and for this reason post-mature confinements should be conducted in hospital. I am convinced that the main risk to the post-mature baby is during labour and that there is always the preliminary warning of foetal distress before death occurs. A careful watch must be kept for this distress, the foetal heart being checked every 10 minutes during the first stage and after every contraction in the second stage. Meconium staining must receive immediate attention, and if there is any reason to suspect foetal distress when the membranes are intact they should be ruptured in a search for meconium. During the conduct of a post-mature labour the operating theatre should be at immediate readiness, and if foetal distress occurs caesarean section should be undertaken at once unless forceps delivery can be easily effected. Babies have frequently inhaled quantities of tenacious liquor amnii before delivery, and endotracheal suction may be a life-saving procedure in these cases.

Those in favour of surgical induction of labour will decry this advocacy of caesarean section. However, giving approximate figures, post-maturity occurs in 7% of patients,

and in this group there is a foetal mortality of 5%. This means that foetal distress due to post-maturity may lead to four caesarean sections in 1,000 confinements, a figure which has been exceeded by several of the writers who advocate surgical induction of labour as the treatment of choice.

Summary

Case reports were obtained from 5,000 patients by means of a personal interview during the first week of the puerperium. These reports showed that in 53.1% of single vertex presentations labour began spontaneously during the 40th or 41st week of pregnancy. In 7.4% the pregnancy was prolonged for more than 14 days after the estimated date of confinement. There was no relationship between the length of the menstrual cycle and the duration of pregnancy, providing that the cycle was not unduly prolonged. There was an increase of foetal mortality to 5.1% if pregnancy was prolonged for more than 14 days after the estimated date of confinement. It is suggested that this mortality resulted from foetal anoxia *in utero*. By reference to a series of 564 stillbirths this foetal anoxia was mainly a risk occurring during the first and second stages of labour. Induction of labour did not appear to be the best means of combating this risk. A policy of "masterly inactivity" is advocated until labour starts spontaneously. Then the strictest watch for foetal distress is indicated, with resort to caesarean section at once in cases in which it occurs.

I am indebted to the honorary medical staffs of the Jubilee and Royal Maternity Hospitals, Belfast, for permission to interview their patients. I wish to acknowledge the encouragement and help which Professor C. H. G. Macafee has given me throughout this work.

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The United Nations is to publish an unabridged record of the International Conference on the Peaceful Uses of Atomic Energy, held at Geneva last month, the Secretary-General has announced. The English language edition will be ready early in 1956. Orders may be placed with any United Nations publications sales agent. The prepublication price for the full series of 16 volumes is £39. Mimeographed copies of most of the individual papers may be ordered through Her Majesty's Stationery Office at 1s. 9d. each.

FOETAL DEATHS FROM ANTENATAL ANTICOAGULANT THERAPY

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The incidence of thrombophlebitis in pregnancy is exceedingly low. Hallum and Newham (1951) reported only five cases of this condition in 13,144 deliveries—an incidence of 0.037%. F. J. Browne (quoted by Donaldson, 1950) saw only three cases in 10 years—an incidence of about 0.025%. Other published figures give an incidence of from 0.000001 to 0.1% (Westmann, 1936). Since, however, considerable success has accompanied the use of anticoagulants in general thrombotic disease and especially in post-partum thrombophlebitis (Davis and Porter, 1944; Barnes and Ervin, 1946; Stallworthy, 1954), their use in the ante-partum variety will inevitably have to be considered whenever a case is encountered.

In spite of experimental data which indicated that damage to the foetus might result from the use of anticoagulants in pregnancy (Quick, 1946) and evidence that foetal haemorrhage occurs in cattle who eat spoiled sweet clover (Schofield, 1924; Roderick and Schalk, 1931), there have been reports of the successful use of anticoagulants in pregnant women (Mansell, 1952; H. P. Wright, 1951; I. S. Wright, 1951). These authors think that there are good reasons for their use so long as adequate control of the prothrombin index is undertaken.

The following case records are reported to indicate that foetal catastrophes may occur even when the maternal prothrombin times are apparently controlled.

Case Histories

The mother was aged 39. Her last menstrual period was on January 11, 1952. The expected date of delivery was October 18, and the actual date October 17. She had had rheumatic fever at 6 years and scarlet fever at 10. She had had three previous pregnancies: (1) 1934, full-term normal delivery, 6 lb. 12 oz. (3.1 kg.), well. (2) 1947, six weeks premature delivery, 4 lb. 4 oz. (1.9 kg.), well. (3) 1949, miscarriage at three months.

During the early months of the present pregnancy there was a marked increase in the varicosity of her leg veins, and on July 14, 1952, she was admitted to hospital because of severe varicose eczema of the left leg. This responded satisfactorily to rest in bed and Lassar's paste. A twin pregnancy was diagnosed at this stage.

Although the varicose veins remained quite prominent the eczema stayed under control, but on October 2 she presented with all the signs of a deep femoral thrombosis of the left leg. She was promptly readmitted to hospital. Treatment included ethyl biscoumacetate 200 mg. immediately, followed by 100 mg. twice daily. On October 4 the dosage was increased to 100 mg. eight-hourly, and this amount was continued until October 9, when, because of macroscopic haematuria, the drug was stopped. The prothrombin time was measured daily by the one-stage method of Quick, and the Table shows the results up to, and after, the cessation of treatment.

On October 16 spontaneous labour started, and after a first stage of 4 hours 50 minutes and a second stage of 1

hour she was delivered of the first boy spontaneously. This was a vertex delivery, but the child was stillborn. The birth weight was 7 lb. 4 oz. (3.3 kg.) and he was noticed to have

Date	Control	Patient	Prothrombin Index
3/10/52	25 secs.	20 secs.	80%
4/10/52	15 ,,	15 ,,	100%
5/10/52	22 ,,	32 ,,	70%
6/10/52	10 ,,	20 ,,	50%
7/10/52	15 ,,	25 ,,	60%
8/10/52	15 ,,	30 ,,	50%
9/10/52	15 ,,	30 ,,	50%
10/10/52	16 ,,	35 ,,	46%
11/10/52	15 ,,	28 ,,	53%
12/10/52	15 ,,	20 ,,	75%

a large head. Thirteen minutes later the second boy was born. The breech presented, but there was no difficulty with the aftercoming head. This child weighed 6 lb. 10 oz. (3 kg.). He was asphyxiated at birth and responded poorly to resuscitation.

Further History of Twin 2

Two hours after delivery he had a brisk haemorrhage from the cord. An extra ligature was applied and vitamin K, 10 mg. six-hourly subcutaneously, was prescribed. At this stage a "blood blister" was observed on his upper lip that had not been present at birth. Although his haemoglobin level after this haemorrhage was found to be 114% his condition never became satisfactory. He became even more feeble; with an irritable, high-pitched cry, and he refused most of the fluids offered him. In addition to the haemorrhagic blister on his lip he developed an apparently spontaneous ecchymosis on the anterior chest wall. At 3 days of age the skull circumference was 14¼ in. (37 cm.) and the sutures were markedly separated. *X*-ray examination of the skull showed marked "starting of the sutures," and in the original films there appeared to be some flakes of calcium present. This could not, however, be shown in further films, and its significance is therefore doubtful. Ventricular puncture revealed the presence of dark-red, heavily blood-stained C.S.F. It was clear that there had been extensive intracranial haemorrhage, and the nature of the C.S.F. indicated that this had probably occurred before birth, since the fluid at 3 days of age already appeared to be "old."

The child's general condition continued to be poor and the hydrocephalus increased. By the age of 13 days the head circumference was 18¾ in. (47.6 cm.). He took feeds badly and gradually lost weight, being a miserable marasmic infant when he died on November 21 at the age of 35 days.

Post-Mortem Reports (Dr. D. E. Price)

Twin 1 (Stillborn).—A little haemorrhagic fluid was present in the nose and mouth. Central nervous system: The right side of the brain was covered by extensive blood clot; the falx cerebri and the tentorium appeared intact; the precise origin of the haemorrhage could not be made out. Cardiovascular system: The pericardium was distended by blood-stained fluid and blood clot; the heart valves and muscle were normal, as were the aorta and other great vessels. Gastro-intestinal system: The stomach contained about 1 oz. (28 ml.) of blood, otherwise there was no abnormality. Testes: Both were surrounded by a blood clot, and extensive haemorrhage into the testicular tissues was present. Lungs: Completely atelectatic, and sank in water. Other systems: No abnormality noted.

Twin 2.—An emaciated male child with marked hydrocephalus. Central nervous system: Extensive internal hydrocephalus; large amount of organizing blood clot at the base of the brain. Lungs: Patchy peribronchial consolidation of the lungs; also pale areas of consolidation pyramidal in shape, with the base towards the pleura; no pleural effusion or adhesions. Other systems: No abnormality noted. Microscopical examination confirmed that the tissue surrounding the base of the brain was organizing blood clot. No calcium deposits were seen microscopically.

Discussion

We believe that both twins died as a result of the anticoagulant therapy given to the mother. There is no doubt that they died of generalized haemorrhages which occurred before birth, and there is no known natural disease which presents in this way. So-called "haemorrhagic disease of the newborn" does not demonstrate itself until after birth. Cerebral haemorrhage of the kind found in the second twin can occur spontaneously, but usually it occurs after a difficult delivery; so far as the first is concerned there seems to be no other explanation of the very widespread bleeding other than the therapy given to the mother. Unfortunately in neither case was a prothrombin time obtained, since the first twin was stillborn and the second twin had already received vitamin K as an emergency measure.

In a survey of the literature we have been able to find only two similar cases. Sachs and Labate (1949) described the case of a woman, seven months pregnant, who had deep femoral thrombosis with multiple pulmonary emboli. She was so improved by the initial dicoumarol therapy that they decided to keep her on it until she was delivered. In spite of keeping her prothrombin time at "about 30 seconds" she had one further, non-fatal, embolism. Twenty days before delivery the foetal heart became inaudible, and eventually she produced, at term, a stillborn macerated foetus. The mother survived. Necropsy on the foetus revealed massive generalized haemorrhages, including a haemopericardium. A similar case was reported by v. Sydow (1947) in which dicoumarol was given for a month and was stopped only two days before delivery, when the prothrombin index (P.I.) was 33% of normal. The baby was born uneventfully but a few hours later developed extensive subcutaneous haemorrhages, and its P.I. was found to be less than 10% of normal. In spite of vitamin K it developed a massive intracranial haemorrhage with subsequent hydrocephalus somewhat similar to that in our second twin.

The fact that anticoagulants could cause haemorrhagic manifestations in the offspring of experimental animals was shown early on by several workers (Field, 1945; Quick, 1946; Kraus *et al.*, 1949), and on the basis of their animal experiments these authors condemned the use of anticoagulants in pregnant women. In spite of this, however, there were a considerable number of reports of their successful use in either single cases or small series (Felder, 1949; Weiss and Turner, 1949; Adamson *et al.*, 1950; Davis, 1951; Thornton, 1951; H. P. Wright, 1951; I. S. Wright, 1951; Mansell, 1952). Most of these authors believe that the danger to the mother may be so great that even in uncomplicated thrombosis the use of anticoagulants is justified. They assert that if the P.I. is properly "controlled" the danger to the foetus is negligible. Most of them recommend that the P.I. should be kept at about 30% of normal. H. P. Wright (1951), however, does extend the warning that anticoagulants should not be used in the "last few days" of pregnancy; and a more recent warning is issued by I. S. Wright *et al.* (1954), who say that their use is contraindicated "in late pregnancy." With this we would heartily agree.

There seems no reason to believe that inaccurate estimations of the P.I. may have played a part in the fatal outcome in our cases. Anticoagulant therapy always carries with it a risk of haemorrhage, and this applies to every substance so far in general use. I. S. Wright *et al.* (1954) reported haemorrhagic incidents in 13% of patients being treated for myocardial infarction by means of anticoagulants. The fact that haemorrhage can occur in the presence of a normal (or only slightly reduced) P.I. is well known, and would appear to be partly explained by Donald *et al.* (1954), who have shown that in certain people the prothrombin, as estimated by the two-stage method of Biggs and Douglas (1953), may be considerably reduced, while by the ordinary one-stage method of Quick it may be only slightly reduced. In these

cases bleeding occurs because of a reduction in true prothrombin, whereas in most cases of haemorrhage due to anticoagulants the bleeding occurs because of depression of Factor VII.

In the case which we describe here the prothrombin time was estimated by the one-stage method of Quick, and it is possible that the maternal and foetal bleeding was due to true prothrombin depression in both. Whatever the anticoagulant employed, however, and whatever method is used to estimate the effect, we shall never be sure that the effect on the foetus is the same as on the mother. It will obviously be safer in the future, if anticoagulant therapy must be used, to rely on both the one-stage and the two-stage methods of estimation, although the one-stage method is still considered to be the best for routine use (Biggs and Douglas, 1953; Donald *et al.*, 1954; Hunter and Walker, 1954).

In order to determine what place anticoagulants should play in the treatment of antenatal thrombophlebitis it is essential to know what is the risk to the mother if they are not given. The incidence of the condition is so low that it is impossible to assess the dangers from such small series as those of Donaldson (1950) and Mansell (1952). One has therefore to turn to thrombophlebitis in general and draw conclusions on what is likely to happen in pregnancy. In several large series mentioned by I. S. Wright (1951), in which the thrombophlebitis was post-operative, the incidence of pulmonary embolism in the diagnosed cases was 50% : where one pulmonary embolism had occurred the incidence of a further, fatal, embolism was 20% (the diagnosis of pulmonary embolism does, however, depend to a great extent on the enthusiasm expended on its detection). In the obstetric cases, most of which must have been post-partum, the incidence of pulmonary embolism in cases diagnosed as having thrombophlebitis was 19–36% and the incidence of a further, fatal, embolism was only 5%. If, in addition, one takes into account Ochsner's differentiation between phlebothrombosis and thrombophlebitis and considers that the latter is by far the commoner in pregnancy and less apt to cause embolism (Ochsner, 1951), it would appear likely that the incidence of fatal pulmonary embolism in antenatal thrombophlebitis, untreated by anticoagulants, is well below 1%. It should be noted, however, that the danger to life is greatly increased after the first embolism has occurred, and also that in about 50% of cases of fatal pulmonary embolism there are no preceding signs of thrombophlebitis (Allen, 1946; Ochsner *et al.*, 1950).

It would appear to us that the danger to the life of a woman with antenatal thrombophlebitis is not sufficiently great to warrant the use of the present anticoagulants as a routine. They should not be used in the last four weeks of pregnancy if at all possible, but if a pregnant woman is having multiple pulmonary emboli then the risk to the foetus will have to be taken and anticoagulants given. Under these circumstances the laboratory control of therapy should be by both the one-stage and the two-stage methods.

Summary

Twin boys of a woman who had received anticoagulant therapy antenatally both died of haemorrhage. It is believed that the foetal haemorrhages resulted from the treatment given to the mother.

Since the risk to the mother from antenatal femoral thrombosis is so small it is recommended that anticoagulant therapy should not be given unless one pulmonary embolism has occurred. This applies especially to the last four weeks of pregnancy.

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Medical Memoranda

Penicillin Anaphylactoid Shock Successfully Treated with Adrenaline

The following cases have occurred within my practice during the period May 12, 1953, to August 8, 1955.

Case 1.—A man aged 75 was suffering from bronchial cancer, although at the time he was thought to have only bronchitis, for which condition a course of injections of crystalline penicillin had been given a year previously, without signs of intolerance. On May 12, 1953, one mega unit of crystalline penicillin was injected into the deltoid muscle. The patient at once complained of severe pain at the site of injection, became pale, sweated, and within a minute his breathing had become stertorous and his colour greyish. Two minutes later he was incapable of speech and pulseless. Adrenaline was now available, and 4 minims (0.24 ml.) of adrenaline 1 : 1,000 was injected subcutaneously. Within fifteen seconds his breathing had improved; in a quarter of an hour he was pale but could speak easily.

Case 2.—A man aged 30–35, a temporary resident, had a dental abscess and a very heavy purulent post-nasal discharge. His temperature was 101.2° F. (38.4° C.). He stated that he had never been treated with penicillin in any form. On June 27, 1953, having adrenaline ready for immediate use, I injected one mega unit of crystalline penicillin into the deltoid. The patient collapsed almost at once, becoming limp, blanched, and pulseless within half a minute. He was immediately given 4 minims (0.24 ml.) of adrenaline 1 : 1,000, and he responded by movement within ten seconds. Injections of 1 minim (0.06 ml.) at intervals of a minute were given for a further five minutes. He spoke naturally after a quarter of an hour. My impression at the time was that, had the adrenaline injection been delayed for perhaps two minutes, the patient might well have died.

Case 3.—A man aged 25–35, a temporary resident, was suffering from an early quinsy. On September 14, 1954, one mega unit of crystalline penicillin was injected into the deltoid, and within a minute he became pale and sweating, the pulse was weak, and he complained of pain at the site of injection. Adrenaline was given and the patient recovered sufficiently to leave the surgery in about a quarter of an hour.

Case 4.—A girl aged 14 had a septic foot. Her mother stated that she had never had an injection of penicillin but that she had been given penicillin lozenges on one occasion without untoward reaction. On August 8, 1955, after one mega unit of crystalline penicillin had been injected into the deltoid, the girl blanched rapidly, sweated, and her pulse

was slowed. She did not lose consciousness and the usual remedies for vaso-vagal attacks were unavailing. After several minutes her condition was the same and adrenaline was injected subcutaneously. Her condition improved only slowly, but the patient stated that she felt better for the second injection. Forty minutes after the penicillin had been injected the girl was still very pale, although her pulse was more rapid and of better volume.

In each of these cases the injection was of crystalline penicillin G alone. Other phials from the same batches did not produce unusual reactions in other patients. It is now, I understand, the general practice not to inject penicillin unless adrenaline 1 : 1,000 is at hand. From my own experiences, it would seem that this is an essential precaution. One other necessary precaution is to inquire carefully into the possibility of an allergic diathesis in patients who have never previously had penicillin.

Morecambe. T. H. TIDSWELL, M.R.C.S., L.R.C.P.

Efficacy of Current Cerumenolytics

Excessive wax formation and retention, or ceruminosis, occurs frequently. If the cerumen is soft, syringeing is rapidly effective ; hard cerumen may be removed by a wax curette. There are a number of cases, however, where cerumen requires preliminary chemical softening before it can be removed. Three cerumenolytics are in general use as an aid to syringeing : sodium bicarbonate and glycerin solution, olive oil, and hydrogen peroxide. Recently an oily preparation, "cerumol," has been produced which is claimed to be ideal for softening, disimpacting, and dissolving cerumen in the external auditory meatus. In spite of the absence of controlled trials this preparation is gaining in popularity.

Since no record of experiments or clinical trials to compare the efficacy of cerumenolytics could be found in the literature an investigation of the relative merits of the four solutions referred to above was conducted by the Royal Air Force E.N.T. survey, which screens entrants into the Service.

PROCEDURE

The four cerumenolytics—sodium bicarbonate ear-drops *B.P.C.*, "cerumol," hydrogen peroxide ear-drops *B.P.C.*, and olive oil *B.P.*—were placed in bottles labelled A, B, C, and D, respectively, with no other distinguishing mark. All the men in a flight were examined otoscopically by a single doctor, flights being dealt with by alternate doctors. When cerumen which obscured an adequate view of the tympanic membrane and which was considered by clinical impression to be hard was present in the meatus of one or both ears the subject concerned was included in the clinical trial. Each such subject was given a paper bearing an indication whether the left or right ear or both ears were affected and was sent into the syringeing room, where five drops of one of the solutions under trial were placed in the meatus and sealed in with a plug of cotton-wool. The four solutions were used in alphabetical order, and every fifth subject was left untreated as a control. At the end of half an hour symptoms of irritation or tingling were noted before the plug was removed and the ear syringed with warm tap water. If longer than five minutes was needed to clear the meatus of cerumen then the cerumenolytic used was considered to have failed. The trial was continued until 37 sets of readings—that is, a total of 185—were obtained. The doctor syringeing the ears was not informed which cerumenolytic, if any, had been used.

RESULTS

The results are summarized in the next column.

Application to the results of the χ^2 test for small numbers shows that only when one of the cerumenolytics—preparation D (olive oil)—was used was the number of occasions on which the meatus was not cleared in the specified time significantly less than when no cerumenolytic was inserted. In other words, only the use of olive oil was significantly better than no treatment at all.

The symptoms of discomfort which were experienced were mainly burning sensations and tingling. Application of the χ^2 test for small numbers shows that symptoms of discomfort due to cerumenolytic B (cerumol) occurred in a significantly greater number of cases than with any other preparation.

Summary of Results

	Cerumenolytic				Untreated
	A	B	C	D	
No. of occasions on which meatus was not cleared within specified time ..	6	7	4	2	9
No. of cases with symptoms of discomfort ..	4	22	6	4	—

I am grateful to the Director-General of Medical Services, Royal Air Force, for permission to publish this paper, and to Dr. H. Cowie and his colleagues, who acted as observers in this investigation.

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Swollen Arms in Infancy

Unilateral swelling of the hand or arm is not uncommon in infants (Illingworth, 1953). Although accepted by many to be a harmless condition, it is still the cause of unnecessary worry both to parents and to doctors who see it for the first time. During the past three years 25 examples of the condition have been seen amongst infants attending the department of child health.

The natural history of the condition shows considerable variation within a broad general pattern. All cases occurred between the ages of 2 and 11 months. The infants have all been in good general health, and there have not been any significant findings in their own or their family histories. With one exception the incidents were observed in the winter months, and there was a particular association with spells of cold weather. The exception occurred in August, 1953. In every case the swelling was noticed in the morning and tended to subside during the day. In a few cases the swelling appeared for one or two consecutive days only ; in others it recurred daily for a few weeks ; in a few it recurred some months later, and in one a year later.

Considerable variation in degree was noted. In some cases one hand only was involved ; in others the arm up to the elbow, and occasionally the whole arm. In a few cases bilateral changes were present, but these were never symmetrical.

The skin was tense and dusky red, or sometimes cyanosed. There was occasionally a slight degree of tenderness, and function was decreased as judged by lack of mobility of the fingers. Seven were in boys and 18 in girls. In all cases the condition cleared spontaneously.

In a search for possible causes of the condition it was observed that there was an impaired percussion note in the infraclavicular region on the affected side. In a few of the cases there was an increase in the mediastinal (? thymic) shadow on the *x*-ray film, but in most there was no radiological abnormality, and it was thought that the impaired percussion note might be due to a degree of associated oedema of the chest wall. The cause of the condition remains uncertain, but the circumstances make it appear likely that it is essentially a peripheral vascular condition precipitated by cold weather.

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Reviews

MICROBIAL PATHOGENICITY

Mechanisms of Microbial Pathogenicity. Fifth Symposium of the Society for General Microbiology held at the Royal Institution, London, April, 1955. (Pp. 333+x. 25s.) Cambridge: For the Society for General Microbiology at the University Press. 1955.

This volume contains the 16 papers which formed the basis of discussion at a two-day symposium held in April last: it was published before the meeting, and hence includes no record of the proceedings themselves. In consideration of the means whereby micro-organisms produce tissue damage pride of place is naturally given to bacterial exotoxins, which are the subject of four papers. That by A. M. Pappenheimer on the pathogenesis of diphtheria perhaps represents the greatest advance in knowledge. We know where toxins act, but little of how they do so; diphtheria toxin is an exception, because there are good reasons —some of them furnished by experiments in silkworm pupae, of all unlikely creatures—for believing that it interferes with the cytochrome system. A minor but interesting discovery in this field is that of the capacity of *gravis* strains to form abundant toxin in a medium of high iron content corresponding to that of the tissues; this is almost certainly the explanation of their greater virulence. By contrast with the results achieved in connexion with this infection, the intensive study of the toxins involved in gas gangrene has so far failed to identify their site and mode of action in producing the systemic effects of this disease.

In the great majority of bacterial infections no such toxin is operative, and our ignorance rather than the organizers of this symposium is to be blamed for the fact that only three papers deal with this much larger subject, the mechanisms at work in infections by such organisms as pneumococci and the *Salmonella, Neisseria,* or *Brucella* groups being entirely disregarded. Of these three papers, one by R. J. Dubos summarizes recent work relating virulence to other properties in *Myco. tuberculosis* and defining conditions within the body which either retard or promote its growth. That by H. Smith and J. Keppie describes work at Porton in which it has been shown that *B. anthracis* growing in the animal body produces a lethal factor not formed *in vitro* and apparently responsible for the vasomotor collapse of the terminal stage of anthrax. The third paper in this trio, by T. W. Burrows, is a study of the nature of virulence in *P. pestis.*

Of the remaining papers on specific subjects, four deal with protozoal infections, one with mycoses, and three with plant disease, all from the same standpoint. Few if any publications of recent times have embodied so much important new work, presented critically by leading authorities who have evidently been self-compelled to reorient their own ideas in doing so. It is to be hoped some of the definitions of terms proposed will henceforth be generally accepted, particularly those of "pathogenicity" and "virulence" suggested by A. A. Miles in the introductory paper.

L. P. GARROD.

MEDICAL PARASITOLOGY

Animal Agents and Vectors of Human Disease. By E. C. Faust, M.A., Ph.D. (Pp. 660; illustrated. 70s.) London: Henry Kimpton. 1955.

The unusual title of this book gives no clue to its scope, but to those familiar with Craig and Faust's well-known and widely used *Clinical Parasitology* a perusal of its contents will suggest that it was probably the author's intention to produce, under a new name, a sixth edition of the original textbook. However, though covering the same ground and including many previous illustrations, the subject matter in the present book is dealt with in quite a different manner. Instead of a comprehensive and systematic account of all known human parasites, the description is restricted to those that are definitely pathogenic, whereas parasites which are not of direct medical importance are only briefly mentioned.

An introductory section, dealing with general parasitological principles, epidemiology, and host–parasite relations, is followed by sections on pathogenic protozoa, nematodes, flatworms, and other helminths. Additional chapters are devoted to arthropods causing and transmitting human disease, and to various other invertebrate and vertebrate animals injurious to man (for example, coelenterates, echinoderms, molluscs, poisonous fishes and snakes). In each chapter a description is given of the structure and life-history of the parasite in question, its pathological effect, symptomatology, and epidemiology of the disease, as well as treatment and prevention. Wide use is made of tables in which all the essential data are brought together in such a way that the symptomatology, differential diagnosis, and other features of the infections can be seen and compared at a glance. The information given in each chapter is condensed in a summary. The book is illustrated by many figures and diagrams, and a final section is devoted to parasitological, cultural, and serological diagnostic methods.

This book will commend itself primarily to medical students and practitioners not specializing in the subject but requiring a reliable elementary guide to the essentials of human parasitology. However, those desiring to amplify their knowledge will find numerous references to other publications. It may be noted here that, in discussing the nomenclature of human entamoebae, Professor Faust—in common with most American authors—refers them to the genus *Endamoeba,* instead of *Entamoeba.* However, it is gratifying to learn that, "should a new opinion be handed down favouring this view, the correct generic name for the species *histolytica* and *coli* will be *Entamoeba.*" Since a ruling to that effect was formally adopted by the International Commission on Zoological Nomenclature in 1951, one may hope that it will now be universally accepted in the United States.

C. A. HOARE.

GLAUCOMA

Glaucoma. A Symposium organized by the Council for International Organizations of Medical Sciences. Editor Sir Stewart Duke-Elder. (Pp. 350; illustrated. 37s. 6d.) Oxford: Blackwell Scientific Publications. 1955.

It was indeed a powerful team that assembled last September upon the Laurentian Mountains, to spend laborious but happy days probing the secrets of primary glaucoma. Papers were delivered concerning aetiological problems, anatomical and biochemical aspects, recent methods of treatment, and up-to-date forms of investigation, including provocative tests. Out of these prepared discourses arose much informal discussion under the chairmanship of Sir Stewart Duke-Elder, who also contributed a preliminary survey of the chief problems and summed up at the close of nearly every debate.

The members of the symposium agreed upon the term "simple" glaucoma to distinguish this disease, or group of diseases, from "closed-angle" (formerly known as "congestive") glaucoma. Nevertheless their deliberations underline the truth that "simple" glaucoma is by no means simple. It is no longer possible for any single person to become expert in all branches of knowledge which have a bearing upon this disease; and it is fatally easy for the whole-time pathologist, biochemist, gonioscopist—and the ordinary clinical ophthalmologist as well—to become preoccupied with his own slant on the problem. The outcome of detailed laboratory work must be linked with facts of heredity, general diathesis, and psychological background, as well as with the results of ocular inspection.

We must not feel undue disappointment that Sir Stewart and his colleagues perforce left many questions unanswered. Some of the explanations accepted in former times were based upon artificial simplification, whereas the contributors

to this volume have faced the difficulties with courage and realism. New methods of investigation and therapy are sanely assessed, and there are some excellent illustrations, especially those which display the vessels communicating with Schlemm's canal. Sir Stewart's aptitude for laboratory research, linked with his own clinical experience and his gift of lucid exposition, has enabled him effectively to sum up the discussions. He was the best possible conductor for this accomplished orchestra.

J. H. DOGGART.

VIRUS DISEASES

Viral and Rickettsial Diseases of the Skin, Eye, and Mucous Membranes of Man. By Harvey Blank, M.D., and Geoffrey Rake, M.B., B.S. Foreword by Donald M. Pillsbury, M.D. (Pp. 285+xiv; illustrated. 60s.) London: J. and A. Churchill Ltd. 1955.

This short but comprehensive textbook on virus diseases is most welcome. Virus infection is responsible for a wide range of affections and is thought to play a role in the causation of very many ills of unknown aetiology. Such ills range from the common infective wart to the exanthemata and meningo-encephalitis. The virus is not always the sole aetiological factor. Still too little is known about viruses or the treatment of diseases for which they are responsible. The authors themselves have done much fundamental work in this field, and they speak with some authority.

Their book is particularly welcome not only because it brings together in simple form most of our knowledge of the nature and causation of virus diseases but because the facts are effectively evaluated and arranged in significant order. This was the objective of the authors, and they have been successful. The clinical presentations are admirable, and many historical facts recorded add to the interest of the work, such as the description of smallpox in China 1200 B.C.

The evidence for cowpox and vaccinia viruses being distinct and the evidence against the herpes simplex virus being responsible for aphthous stomatitis in the infant are set out. The earliest clinical manifestation of the herpes simplex virus is generally a gingivo-stomatitis. Questions of infectivity and immunity are discussed, as is the viability of viruses away from the host. The authors emphasize that the risk of vaccinating the eczematous is the development of varicelliform dermatoses which may prove fatal. The section on warts is excellent, and the authors do not disregard the part played by suggestion in the development and treatment of these troublesome lesions. There is a very good description of milkers' nodules and discussion of the differential diagnosis. Indeed, this book will serve student, general practitioner, and specialist as an excellent reference for the description of the clinical features of the common virus diseases included in it.

J. T. INGRAM.

MENTAL MEASUREMENT

An Introduction to Mental Measurement and its Applications. By C. A. Richardson, C.B., M.A. (Pp. 102+viii. 8s. 6d.) London, New York, Toronto: Longmans, Green and Co. 1955.

Mr. Richardson's object has been to explain, in simple and non-technical language, the purposes and principles of psychological measurement, and to discuss how far they are fulfilled by existing tests. The opposition to such methods, he believes, is largely due to the fact that those who invent or advocate them adopt a predominantly statistical approach which is often repugnant and usually unintelligible to all but the mathematical specialist. He has therefore endeavoured to explain the basic concepts—scales, units, intelligence quotients, grading schemes, and the like—in ordinary common-sense terms. As he himself was for long one of the Ministry of Education's Chief Inspectors, he is thoroughly familiar with the problems which have led to the introduction of mental and scholastic tests in schools and with the inevitable limitations of all such procedures.

He briefly traces the history of psychological measurement, from the early introduction of tests of sensory discrimination, like those for visual and auditory acuity, to the more ambitious "group tests" for measuring general intelligence and specific aptitudes. This is followed by a detailed discussion of "the factors of the mind," though here he apparently attributes to Spearman much that Spearman avowedly borrowed from Galton. The most valuable parts of this book are the chapters on "practical applications" such as the importance of the I.Q. in the diagnosis of the educationally subnormal, the help given by tests in allocating pupils to different types of secondary school under the 1944 Act, and the value of objective methods of assessment for purposes of vocational guidance.

This manual should provide a useful introduction, not only for teachers and students of psychology, but also for school medical officers and psychiatric specialists who wish to familiarize themselves with these quantitative procedures.

CYRIL BURT.

FRACTURES AND JOINT INJURIES

Fractures and Joint Injuries. By Sir Reginald Watson-Jones, F.R.C.S., M.Ch.Orth. Volume II. Fourth edition. (Pp. 445–1073; illustrated. £6 per set.) Edinburgh and London: E. and S. Livingstone Ltd. 1955.

The fourth edition of the second volume of this work follows three years after that of the first. The contents include injuries of the upper and lower limbs and trunk, and the subject matter has been brought up to date twelve years after the last edition. There are copious indices, and at the end of Part V, which deals primarily with trunk injuries, are two most important chapters. Every surgeon dealing with trauma should study both of them, one being on the organization of an accident service and the other on the principles of rehabilitation after fracture and joint injuries. No one is better qualified to teach and write on these subjects than the author, and possibly in a future edition they can be given greater prominence.

The description of each injury is very lucid, and any not mentioned must be very rare. The slight alterations and additions are made to fall into line with the high standard of which readers of previous volumes were appreciative. The space given to each injury is well planned. The surgeon in difficulty will find alternative methods of treatment—particularly for the injuries apt to cause anxiety, such as fracture of the femoral neck, of the tibial shaft, or of both forearm bones, as well as those into joints. The reader will appreciate the value of the dogmatic description and excellent advice regarding dangers of treatment carried out incorrectly or under conditions unsuitable for first-class work.

The illustrations are excellent—not only well chosen and of the highest quality, but most helpful when dealing with the injury depicted. Readers will delight in the retention of the illustration depicting the author reducing a shoulder dislocation by the Hippocratic method. This and the sister volume have well deserved the international reputation of being accurate, concise, and convenient. It is important that such unrivalled books should be available for reference in every institution where injured patients are treated. The author and publishers are to be congratulated on the high standard of the book.

ST. J. D. BUXTON.

In 1948 the Family Welfare Association set up the Family Discussion Bureau run by trained social caseworkers. *Social Casework in Marital Problems: The Development of a Psychodynamic Approach* is an assessment of the work of this Bureau over the first five years. It explains the aims of the Bureau, the training of the case workers, and the basic problems with which they have to contend. A number of detailed case histories have been carefully selected to show the wide range of people who have come to the Bureau for help and the variety of problems, both psychological and otherwise, which a case worker may have to face. Finally there is a chapter discussing the Bureau as a social agency and a useful reading list on psychiatric social work. The book is published by Tavistock Publications Ltd., price 15s.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY SEPTEMBER 17 1955

CORTISONE AND ASPIRIN

Rheumatoid arthritis is a comparatively common disease affecting, if we are to generalize from the results of the Leigh survey,[1] between 1 and 3% of the population, and every general practice includes a number of such patients. Their management is often a problem. While some patients go into remission and remain well over long periods of time with or without treatment, others—and these are in the majority—become in the course of years moderately disabled, and some go progressively downhill despite all efforts of their physicians. All specifics introduced for its treatment so far have passed through three stages: the stage of enthusiastic welcome, the longer stage of practical large-scale use and gradual waning of enthusiasm, and then a final phase where such measures are used really only for want of anything better and until the next new substance comes along. Thus, although vaccine treatment superseded spa treatment and mud packs, gold treatment later superseded vaccines, and cortisone superseded gold, to-day throughout the world cortisone, vaccine, gold, aspirin, and physiotherapy are used side by side. This process is largely one of fashion: objective assessment demands more time and care than can easily be spared by the busy practitioner. Thus a heavy responsibility rests with those to whom he looks for guidance.

Over a year ago there was reported in this *Journal*[2] the outcome of a year's treatment of 61 patients in the early stages of this disease, drawn from six centres in England and Scotland. The report was the work of a Joint Committee of the Medical Research Council and the Nuffield Foundation. The patients had been divided by random allocation into two groups, one being treated with cortisone and the other with aspirin; and both received such adjuvant measures (for example, physiotherapy and splintage) as were considered necessary. At the start of the trial the two groups were almost identical in all important respects, as indeed it was planned they should be. At three points during and also at the end of the year it was found that the two treatment groups were still almost identical. Improvement in functional capacity had occurred in each group and to a similar extent: thus initially only 4 of the 30 cortisone and 5 of the aspirin patients were fully or partially employed, while by the end of the year 23 out of the 30 patients on cortisone were so employed and 21 out of the 26 patients remaining in the aspirin group. Similar improvement was seen in other indices—disease activity, joint tenderness, range of movement, strength of grip, and sedimentation rate. Only one measurement showed an unequivocal improvement on cortisone that was not seen in the aspirin group—the haemoglobin content of the blood.

These patients have now been treated and followed for a further year, and in our opening pages this week the Joint Committee reports that the improvement seen during the first year has been maintained in both groups. At the end of this second year, "in no respect do the two groups differ by more than might easily be due to chance"—even, in this second year, in respect of the haemoglobin figure. With the dosage used, the improvement seen in the patients on aspirin is equal to that in the patients on cortisone, no matter what criteria of improvement are selected. This result might be a matter of dosage level—that is, the amount of cortisone given might not have been adequate—but the mean maintenance value of 80 mg. per day at the end of the first year and 75 mg. per day at the end of the second year is as much as has been given in most of the reported series, however good were the results claimed. Certainly most clinicians in the U.S.A. and in this country would agree that this is a reasonable mean level for "the minimum dosage that would restore maximal functional efficiency without producing serious side effects," which was the guidance given on maintenance dosage to the physicians participating in the trial. Only one patient in the cortisone group suffered side effects serious enough to cause discontinuance of treatment.

Of particular interest in this present report are the *x*-ray findings. While there was some difference between observers in the assessment of osteoporosis and erosions, at the end of the two years a rather higher (but not significantly higher) incidence of erosion was seen in the aspirin group. Confining attention to those patients in the aspirin group who had initial radiographs taken and a similar matching number in the cortisone group, the committee found that while at the beginning only 6% of each group showed erosions, at the end of the two years 65% of the cortisone and 74% of the aspirin group

[1] Kellgren, J. H., Lawrence, J. S., and Aitken-Swan, J., *Ann. rheum. Dis.*, 1953, **12**, 5.
[2] *British Medical Journal*, 1954, **1**, 1223.
[3] Ibid., 1954, **1**, 233.
[4] Ibid., 1955, **1**, 555.
[5] Ibid., 1955, **1**, 1520.
[6] Dordick, J. R., and Gluck, E. J., *J. Amer. med. Ass.*, 1955, **158**, 166.
[7] Bunim, J. J., Pechet, M. M., and Bollet, A. J., ibid., 1955, **157**, 311.
[8] Margolis, H. M., Barr, J. H., Jr., Stolzer, B. L., Eisenbeis, C. H., Jr., and Martz, E. W., Jr., ibid., 1955, **158**, 454.
[9] Bollet, A. J., Black, R., and Bunim, J. J., ibid., 1955, **158**, 459.
[10] Hollander, J. L., Brown, E. M., Jr., Jessar, R. A., Udell, L., Smukler, N. M., and Bowie, M. A., ibid., 1955, **158**, 476.

showed such residual effects of the disease. It is clear, therefore, at least in the early stages of this disease when it was once thought that the effect of cortisone would be the most valuable, that, while individual patients may respond better to aspirin or to cortisone, on the whole there is little to choose between the two drugs—a conclusion similar to that reached by the same committee studying their effects as adjuvants to manipulation in rheumatoid arthritis,[3] and similar also to the conclusions reached for a somewhat different disease in the co-operative clinical trial[4] of A.C.T.H., cortisone, and aspirin in rheumatic fever carried out by physicians in the United Kingdom and in the U.S.A.

This is not to decry the value of hormones in selected cases of rheumatoid arthritis, still less so in the wider field of therapeutic medicine and research, where these and related synthetic hormones are only at the start of a long career of great value. Within the field of rheumatoid arthritis it is possible that one day physicians may be able to distinguish those patients who will respond better to cortisone than to the traditional aspirin, but at the moment they cannot do this apart from trying both drugs in a cross-over type of trial. The results of the Empire Rheumatism Council's trial of cortisone versus aspirin in the treatment of established cases of rheumatoid arthritis will be awaited with great interest. Meanwhile there is still the possibility that the newer analogues—such, for instance, as metacortandracin and metacortandralone, on which we commented recently[5]—may make it possible to give higher doses to reduce inflammation without increasing the incidence of side effects.[6–8] Although undoubtedly they cause less water and salt retention, it is not yet known whether hypertension will be less frequent with the new drugs; certainly from preliminary reports the development of peptic ulcer and dyspepsia seems to be a major drawback.[9] The local use of hydrocortisone by injection into inflamed rheumatoid joints is undoubtedly useful and has had a limited success. Its main disadvantage is that its effects usually last for one or at most two weeks, and it is impossible from purely practical considerations to inject joints week in, week out, for life. Again a major practical advance may result from the introduction of analogues with a prolonged action, the first of which is hydrocortisone tertiary butyl acetate.[10] It is to be hoped that these newer substances will each be subjected to the same careful and painstaking comparison with the older established methods of treatment that has been carried out in this country for cortisone.

FOETAL DISTRESS

The signs of foetal distress during labour are usually those of intrauterine asphyxia. The syndrome is so commonly encountered in practice that it deserves more attention than has been accorded to it in the literature. In a recent issue of this *Journal* T. B. FitzGerald and C. N. McFarlane,[1] using fairly wide criteria, noted an incidence of foetal distress of 6.5% in a series of just over 3,000 deliveries. They regarded slowing of the foetal heart rate to less than 110 beats per minute, or even a relatively considerable drop to 120, as significant. The usually accepted indication of foetal distress is a rate below 100. Less important, though not lightly to be dismissed, is a rise to over 160 per minute, and it would appear to make little difference whether the rise precedes the fall or vice versa. Arrhythmias and marked variation in rate, even though provoked by uterine contraction, nevertheless indicate a threat. The passage of meconium is always ominous, especially if freshly passed, as compared with old staining.

In enlightened modern obstetrics, foetal death during labour is far more often caused by intrauterine anoxia than by trauma. The age of the mother does not appear to make much difference, but foetal distress is almost twice as common in the primigravida, owing to the higher uterine tone between contractions. Hypertonic types of inertia, including the "colicky uterus," likewise carry a worse foetal prognosis in this respect, and the evils of prolonged labour, so far as they affect the foetus, are directly proportional to the time that has elapsed since the membranes ruptured. Pre-eclamptic toxaemia and hypertensive states, by their known association with a reduced maternal placental blood flow, to say nothing of infarction, also bring the placenta nearer to the limits of its oxygen reserve. The role of mechanical factors is obvious—as, for example, in placental separation from any cause, or obstruction to the circulation in the umbilical cord due to tight winding round the neck, knotting, presentation, prolapse, or undue shortness. J. Stallworthy, in a recent letter to this *Journal*,[2] reminds us that if the rate and rhythm of the foetal heart are affected by pressing the unengaged head into the pelvic brim during the last trimester the obstetrician should consider the possibility of a posteriorly situated placenta praevia with low insertion of the cord or perhaps some degree of

[1] FitzGerald, T. B., and McFarlane, C. N., *British Medical Journal*, 1955, **2**, 358.
[2] Stallworthy, J., ibid., 1955, **2**, 488.
[3] Walker, J., and Turnbull, E. P. N., *Lancet*, 1953, **2**, 312.
[4] Donald, I., *J. Obstet. Gynaec. Brit. Emp.*, 1954, **61**, 725.
[5] Walker, J., ibid., 1954, **61**, 162.
[6] Holmes, J. A., and Payne, J. A., *British Medical Journal*, 1955, **1**, 1071.
[7] Donald, I., *Practical Obstetric Problems*, 1955, London.

cord presentation. He has also noted that the foetal heart rate may fall below 100 per minute during entry of the head into the brim in the course of trial of labour, followed thereafter by recovery. Analgesic drugs commonly given to the mother during labour seldom cause foetal asphyxia, though they commonly depress respiratory activity after birth; but drugs which have been used in the past to expedite labour, such as quinine and posterior pituitary extracts, readily provoke signs of foetal distress.

Prolonged pregnancy is now fairly widely accepted as a cause of foetal anoxia, with a consequent rise in perinatal mortality. J. Walker and E. P. N. Turnbull[3] have noted a gradual fall in the oxygen content and saturation of the foetal blood with the approach of term associated with a rise in haemoglobin and red cell levels, suggesting that the child is beginning to out-distance its oxygen supply. This trend is accentuated after forty-one weeks' gestation. In this issue of the *Journal* (p. 715) Mr. G. B. Gibson, in an analysis of 5,000 deliveries, reports that he found pregnancy was prolonged in 7.4%, with a perinatal mortality of 5.1% in these cases, the minimal rate (about 2%) in the 41st and 42nd weeks being doubled in the 43rd week and trebled thereafter. The higher incidence of operative delivery inevitably associated with postmature labour also goes with an increased incidence of foetal distress—though cause and effect must not be confused. Difficulty and delay in delivering the large shoulders of the postmature baby also account for some disasters. Gibson finds that the postmature baby is mainly at risk during labour itself, and considers that it causes no more anxiety than other babies once respiration has been satisfactorily established after birth. These babies are often almost choked with meconium and liquor prematurely inspired, and yet, as I. Donald[4] has pointed out, atelectasis with hyaline membrane is exceedingly rare in the postmature.

Many would agree with Gibson's condemnation of the "rigours of castor oil which so often accompany the forty-first week of pregnancy"; yet, if we are to accept postmaturity as a cause of foetal distress, it is surprising how widely authorities differ in acknowledging the need to forestall it by the induction of labour. J. Walker,[5] for example, has recommended surgical induction in primigravidae over the age of 25 who have outrun their dates by five to seven days, but Gibson induced only thirteen of his cases on grounds of postmaturity. He advocates hospital confinement of such cases, intense vigilance for foetal distress, and immediate delivery by forceps or caesarean section, as appropriate, as soon as it appears. Nevertheless, foetal distress is not merely a threat but an established fact, and it is unfortunate that foetal asphyxia cannot be more readily and accurately foreseen. The severity of the signs, moreover, is by no means proportional to the degree of anoxia.

To put off action once foetal distress is recognized is to imperil further the life of the infant. Particularly distressing are those cases in which the foetal heart stops suddenly without apparent warning, but FitzGerald and McFarlane have observed that, though 37% of their stillborn infants died during labour, in the 26 cases in which the signs were properly looked for only three died without warning, and the foetal mortality was halved in the cases where early intervention was adopted. Unfortunately, observation of the foetal heart every ten minutes in the first stage and after every uterine contraction in the second, as recommended by Gibson, is not easy to carry out in more than a few selected cases, and the selection itself may be faulty. The patient is not only disturbed but may naturally become alarmed, and there is clearly a need for a reliable apparatus for automatically monitoring the foetal heart. As soon as foetal distress appears, nitrous oxide and air analgesia should be stopped and the mother should be given pure oxygen to breathe; this is only a temporary measure while arrangements for speedy delivery are put in hand, and the medical attendant should not be lulled into inaction by the temporary improvement which oxygen sometimes brings. If the cervix is fully dilated the obstetric forceps may be life-saving, and in such cases an episiotomy will reduce birth trauma to a baby already in distress. Even so, after delivery foetal shock (pallid asphyxia) may be so pronounced, owing to anoxic depression of the vital centres, that the baby's condition for the time being may be indistinguishable from that due to intracranial haemorrhage.

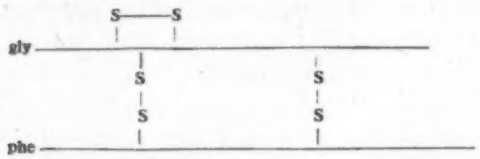
The resuscitation of the severely asphyxiated baby is often a desperate emergency, yet even now there is considerable disagreement about the measures to be adopted. These vary from oxygen, warmth, and hoping for the best on the one hand to electronically controlled respirators such as Donald's at the other extreme. As the minutes go by before respiration is established, the damage which the child's central nervous system may be suffering can be only a matter for gloomy conjecture. Irreversible harm may be done within twenty minutes, and yet in other cases there is a surprisingly happy outcome. Recently J. A. Holmes and J. A. Payne[6] recorded a case of apparently complete recovery, followed up for over eighteen months, in which the child did not spontaneously breathe for 140 minutes. It would appear that so long as the heart continues beating the child should have the benefit of the doubt. It is not yet possible to relate

the child's subsequent intellectual capacity to the degree and duration of asphyxia suffered at birth. Nevertheless, "it is as well to assume that in resuscitating the newborn, one is fighting not only for the child's life but for its very wits."[7] No technique of resuscitation at birth could achieve as much as the prevention of the need for it in the first place.

THE INSULIN MOLECULE

Two publications reporting work that settled the chemical constitution of vitamin B_{12} (cyanocobalamin) have already been the subject of comment in this *Journal*.[1] They came out some fourteen days after another paper[2] in which was recorded what many will regard as perhaps an even greater triumph of modern British chemistry. Dr. F. Sanger and his colleagues in the Department of Biochemistry at Cambridge have now presented us with a complete picture of the insulin molecule—17 amino-acids, each different one present from six times down to once, giving a total of 48 individual units, with an empirical formula of $C_{254}H_{377}O_{75}N_{65}S_6$, a total of 777 atoms per molecule and a molecular weight of 5733.5.

The Cambridge team's first paper on this subject appeared in 1945,[3] so that their work has taken ten years to bring to its successful fruition—not a long time in view of the problem's complex nature. Dr. Sanger gave an indication of their final conclusion as long ago as June, 1954, when he told the Biochemical Society[4] that insulin must have a structure that could be represented as



Here "gly" and "phe" represent terminal glycine and phenylalanine residues; the sulphur-bridges are parts of three separate cystine residues, and the two parallel lines represent straight polypeptide chains. The full paper now available[2] makes it clear that the upper chain contains 21 units and the lower chain 30 (counting each cystine residue as two cysteine units).

There are many interesting, and some surprising, features about the nature and arrangement of the amino-acid residues present. All amino-acid residues occupy the same length in a polypeptide chain, their differences being expressed as different "side-chains." The arrangement is much as in feathers: the rachis may be identical in different ones, but the pattern is made by the plumules. It is clear from the now known structure of insulin that the two long sides of the "ring"—shown on the diagram as a rectangle including four sulphur atoms—do not contain the same number of residues, so that they must be of unequal lengths. This confirms, what is already indicated by other considerations, that the insulin molecule must be coiled or askew in some other way.

Neither tryptophan nor methionine is present. Five amino-acids—arginine, isoleucine, lysine, proline, and threonine—occur only once, histidine twice, and there are three units each of asparagine, alanine, cystine, glutamine, phenylalanine, and serine. The most frequently occurring units are those of leucine (six times), valine (five times), and glutamic acid, glycine, and tyrosine (four times each). How the exact arrangement of these units in the two chains was determined is described in 79 pages (6 papers) in the *Biochemical Journal* and in one and a half pages of the *Proceedings of the Biochemical Society*, beginning[4] in 1954 and ending[2] in 1955. Other papers by the same authors show how the methods they developed have been applied to the study of different proteins and of "model" polypeptides. Complementary work published during the same period by Dodds, Butler, and their colleagues at the Courtauld Institute has helped to make the intricacies of the insulin molecule steadily clearer.

In a separate paper[5] the Cambridge workers record another result that may lead to much speculation. Apparently there are minor differences between the glycyl chains of different insulins; in the 8–10 positions of this chain insulin from cattle has alanine–serine–valine (as shown for the whole insulin molecule in the main paper), whereas pig insulin has threonine–serine–isoleucine, and sheep insulin has alanine–glycine–valine. Apart from the fact that these differences will slightly affect formulas and molecular weight, they must be viewed as part of the whole vast problem of the species specificity of proteins.

The Cambridge workers point out in their latest publication that the "ring" is "the same size as the similar disulphide ring found in oxytocin . . . and vasopressin . . .," two proteins with important normal physiological functions to perform. Their structure has been elucidated, and they have indeed been synthesized, by du Vigneaud and his team at Cornell University.

All work of this nature, however remote it may appear and even prove to be for practical therapeutic

[1] *British Medical Journal*, 1955, **2**, 610.
[2] Ryle, A. P., Sanger, F., Smith, L. F., and Kitai, Ruth, *Biochem. J.*, 1955, **60**, 541.
[3] Sanger, F., ibid., 1945, **39**, 507.
[4] —— Smith, L. F., and Kitai, Ruth, ibid., 1954, **58**; *Proc. Biochem. Soc.*, vi.
[5] Brown, H., Sanger, F., and Kitai, Ruth, ibid., 1955, **60**, 556.
[6] Medical Research Council. Report for the Year 1953–1954, p. 4. H.M.S.O., London.

applications, should be vigorously supported by the medical profession for reasons of at least three different kinds. Knowledge of structure is essential to the performance of synthesis. Synthesis may in favourable circumstances oust biological production or extraction from natural sources; it has done so for chloramphenicol, though not for penicillin. Riboflavine and tocopherol are made sometimes one way, sometimes the other. Though the posterior pituitary factors have been synthesized, they are likely, as are insulin and vitamin B_{12}, to go on being produced biologically for the immediately predictable future. But even so, precise knowledge of structure may often turn out to be helpful; thus it has made possible an increase in yields of benzylpenicillin at the expense of the less wanted analogues by "feeding the brute" on sources of the benzyl radicle. Secondly, exercises in this kind of analytical chemistry, involving not only great manipulative skill in laboratory technique but also extremely close logical thinking for both planning and interpreting experiments, provide just the right stimulus for the sturdy health and progress of chemistry as a sister science to physiology and pathology. The 1954 report[6] of the Medical Research Council is eloquent on the need for sororal relations of this kind. Thirdly, knowledge of structure is an essential prerequisite to any full understanding of biogenesis, of normal physiological functions, and of both preventive and curative use—whether it be for genuine replacement therapy or for palliation.

It is at least reasonable to expect that the prospects for cure and prevention will have been substantially advanced because of the work of Cambridge biochemists, which has shown us just what insulin is, and that of the Cambridge chemists, Oxford crystallographers, Greenford biochemists, and American cybernetists, which has done the same for vitamin B_{12}.

FOOD AND WORK

In the ordinary way of life the amount of food eaten varies in relation to physical activity, and dietary needs are largely determined by occupation. Attempts to classify different types of activity in terms of calorie requirements have been handicapped in the past by lack of an efficient method of assessing the metabolic activity of subjects engaged in laborious occupations. Many of the energy requirements of different workers listed in the textbooks on physiology are of doubtful accuracy, since the measurements had to be made while the subject was working harnessed to a Douglas bag or enclosed in a human calorimeter. A lumberjack or miner cannot work normally under such conditions. Moreover, increasing mechanization and shorter hours have almost certainly made a difference in the total expenditure of energy in many occupations. In 1951 the Medical Research Council appointed a committee to investigate the problems of diet and energy requirements in present-day occupations.

It was decided to carry out initial studies on the coal-mining industry, which employs both manual and sedentary workers. Fortunately at this time a respirometer weighing only 6½ lb. (3 kg.) was developed by Kofranyi and Michaelis at the Max Planck Institut für Arbeitsphysiologie in Dortmund. This can be worn like a haversack and records the volume of expired air, simultaneously ejecting a sample of this air into an attached rubber bag, from which it can be subsequently withdrawn for analysis. Using this machine a team of workers from the Diet and Energy Committee of the M.R.C. and the Ministry of Food carried out a survey in a Fife coalfield. Their findings have recently been published.[1] The respirometer was used to find, in terms of calories per minute, the metabolic cost to each subject of the majority of everyday activities under normal working and resting conditions. Energy expenditure during the twenty-four hours was calculated for each man for seven days. At the same time the food intake was carefully recorded.

The total daily expenditure of energy of the miners, all of whom were performing hard physical labour during their working hours, was on the average 3,660 calories a day; that of the clerks was 2,800 calories. The two groups expended approximately 1,750 and 890 calories a day respectively at work. Whilst at rest and off duty and at home the two groups of workers had an almost identical expenditure of energy. In their spare time the miners were no more energetic than the clerks. They slept or dozed two or three hours a day, and spent most of the remainder of the time reading or playing with their children, or taking short walks. Two-thirds of their total time, at work and at home, and one-third of their total energy was spent sitting or recumbent. Their activities when not at work consumed 1,420 calories, which was practically the same figure as for the clerks.

The miners spent 38% of the time underground in the mine sitting about. The metabolic cost of the various mining activities was about 7 calories per minute, but the mean rate of energy expenditure during the entire time spent at work underground was only 4.3 calories per minute. This is not to suggest that the miners did not work hard; numerous interruptions and time spent walking to the coalface accounted for the difference between the two figures. The intake of energy in the form of food reflected the difference in the expenditure of energy of the miners and clerks. The miners took in 990 more calories than the clerks each day. Although the miners obtained many more calories from their diets than did the clerks the percentages of calories derived from protein, from fat, and from carbohydrate were essentially the same in the two groups. There was

[1] Garry, R. C., Passmore, R., Warnock, G. M., and Durnin, J. V. G. A., "Studies on Expenditure of Energy and Consumption of Food by Miners and Clerks, Fife, Scotland, 1952." *Spec. Rep. Ser. med. Res. Coun. Lond.*, 1955, No. 289, H.M.S.O., London. Price 5s. net.

no suggestion that the miners drew the additional energy required for their hard physical work from carbohydrate foods. They ate more than the clerks of nearly all foods, and ate more on their working days than on their off days. Apart from the riboflavine intake the amount of all other nutrients seemed adequate in the two groups of workers.

SICKNESS AND MORTALITY RECORDS

Three subjects—general morbidity, cancer, and mental health—are discussed in a supplement[1] published this week to the Registrar-General's *Statistical Review* of England and Wales for the two years 1950 and 1951. The same subjects were discussed in a similar review[2] covering the year 1949 which was published early last year. So far as morbidity is concerned, the official Survey of Sickness, begun in 1944, was suspended early in 1952, and the present volume carries the account of the Survey to its close. The figures show that the epidemic of influenza in 1951 affected men over 65 more than any other group of the population: the prevalence of the disease among them was more than double that in 1949, when there was a mild outbreak. At all ages the duration of incapacity and the number of medical consultations for influenza increased in 1951, as compared with 1949, even more than the prevalence, and thus the cases were probably more serious as well as being more numerous.

The section on cancer registration continues for the fifth year the account of those cases of cancer which were first registered in 1945 and 1946. These cases form only about one-quarter of the estimated total in these years, but in later years this proportion more than doubled, and in 1954 registration in some areas was nearly complete. The analysis of the cases registered in 1945 and 1946 can therefore be regarded as an early chapter in the more complete natural history of cancer which is being built up from the cancer registration scheme. In this volume four sites are selected for special study—the female breast, the cervix uteri, the rectum, and the skin. Age distribution and survival rates are recorded. The corrected 5-year survival rates for patients with primary cancers, without secondaries, treated radically were for cancer of the breast 67%, for cancer of the cervix uteri 51%, for cancer of the rectum 50%, and for epithelioma of the skin over 80%. The report comments on the rather curious picture given by analysis of the survival rates of patients with cancer of the breast: "In each age group the survival rate bears no relation whatsoever to the interval before treatment. Especially among the late primary cases patients appear to have a better chance if they are treated either before three months have elapsed from the appearance of the first symptom or if the growth has existed for more than a year." This is in line with figures which have been published elsewhere. The survival rate for patients with early primary carcinoma of the breast, with no secondary nodes or metastases, is much higher in those between the ages 45–49 than in any other age group. A somewhat similar picture emerges from the analysis of cases of cancer of the cervix uteri: the chances of survival appear to improve with the length of history in certain age groups, irrespective of whether the disease is first seen in an early or later stage. Again, in so far as cancer of the rectum is concerned, "the only conclusion that can be drawn is that the chances of survival are not directly related to the time elapsing between the onset of the first symptom and the commencement of treatment."

The section of the review on the subject of mental health continues the study of the illnesses of patients in mental and mental deficiency hospitals. In 1951 both the East Anglian and Welsh regions had reached the position in which at least 75% of both male and female admissions were of voluntary patients. The admission rate to mental hospitals for psychoses was much higher for social class V (unskilled occupations) than for any other class, but the admission rate for alcoholism was much greater for social class I (professional and administrative). Among the many interesting pieces of information recorded in this section was the finding that those women who said they had no religion had the lowest proportion of admission for psychoses and the highest proportion for neuroses.

ROYAL COLLEGE OF MIDWIVES

It was in 1881 that Miss Louisa Hubbard and a small group of women banded together and founded the Midwives Institute with a view to "raising the efficiency and improving the status of midwifery," so that the mothers and babies of this country could get the better care they so sorely needed. But even these far-sighted women could scarcely have visualized how much was to come from such small beginnings, or that their Institute would grow to a Royal College with a membership of 10,000 trained professional women. At page 738 of this issue we print a letter from Mr. C. S. B. Wentworth-Stanley calling attention to a national appeal for funds for a new building for the headquarters of the Royal College of Midwives. The present premises, he writes, "are quite inadequate for the purposes and needs of the College of Midwives." In particular, an appeal leaflet says, there is a pressing need for an extension of educational facilities for which there is a student demand in excess even of the 2,000 who already pass through the College. When this educational work is viewed in relation to the fact that some 80% of all deliveries in this country are conducted by midwives, its importance may be realized. Gratitude for happy events safely accomplished will undoubtedly show itself in responses to this appeal from homes all over the country; and the medical profession will not be least in its consciousness of the debt it owes to its midwife colleagues, who clearly cannot themselves find all of the £150,000 required.

[1] *Registrar-General's Statistical Review of England and Wales for the Two Years 1950–1951: Supplement on General Morbidity, Cancer, and Mental Health*, 1955, H.M.S.O., London. Price 8s. 6d. net.

[2] *Registrar-General's Statistical Review of England and Wales for year 1949: Supplement on General Morbidity, Cancer, and Mental Healt*' 1954, H.M.S.O., London. See annotation in *British Medical Journal*, 1954, 1, 88.

EMERGENCIES IN GENERAL PRACTICE

ACUTE RHEUMATIC FEVER

BY

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Rheumatic fever belongs to the group of disorders now classed as collagen diseases in which there is damage to collagen fibres and connective-tissue structures. In the last few decades there have been several slow and subtle changes in the manifestations and incidence of this disease. Although it may present the familiar picture of high fever, flitting joint pains, and prostration, it is now more often a condition with an insidious onset, unassociated with fever, and in at least 10% of cases with no history of joint involvement. Because of this variability and because most cases have their onset in childhood, the use of Miller's term "juvenile rheumatism" in preference to acute rheumatic fever has much to commend it.

Various writers have drawn attention to the fact that the incidence of acute rheumatic fever goes parallel with that of scarlet fever, and there has been a steady decline in the incidence of both diseases which began about the turn of the century. Since 1935, however, the fall has been accentuated, and it is a moot point whether or not the introduction of sulphonamide therapy into general use has played a part. In 1928 the deaths recorded in England and Wales from rheumatic fever were 1,500, in 1938 1,135, and in 1948 446. As morbidity goes parallel with mortality, these figures will serve as an indication of the extent of the diminution in the incidence of the disease. Rheumatism and its treatment and prevention, however, still remain important public health problems.

There is general agreement that rheumatism is related in some way to infection, usually in the throat, with Group A beta-haemolytic streptococci. By no means all subjects infected with this particular strain of streptococci suffer from rheumatism, but for some reason as yet unknown a subject may become "sensitized" to it: he is then a rheumatic subject and prone to recurrent attacks.

Clinical Findings

Rheumatism is very rare in children under 3 years of age and uncommon even in those under 5 years. The acute fulminating type of case is still seen occasionally and can be an emergency in general practice, but the more usual story is of a sore throat with perhaps some constitutional disturbance which is followed by a latent period of 14 to 21 days; then, with malaise, fever, and anorexia, vague joint pains make their appearance. The joints are painful on movement; there will be some slight swelling but seldom redness. The flitting and fleeting nature of this joint mischief is often marked. It responds dramatically to adequate dosage of salicylate but will also disappear without treatment.

Heart.—Carditis is the only crippling manifestation of rheumatism. The lesions may vary from mild enlargement and a mitral systolic murmur to gross enlargement with obvious involvement of both mitral and aortic valves. Presumably in every case of acute rheumatism there will be some myocardial involvement whether it can be detected or not, and the congestive failure seen in the acute phase of the disease is due to myocardial involvement rather than to valvular damage. The fully developed clinical picture of mitral stenosis with or without auricular fibrillation is rarely encountered before the fourteenth year. Pericarditis is undoubtedly the most serious of the cardiac lesions and is often associated with other evidence of the massiveness of the attack, such as subcutaneous nodules, fever, cyanosis, and prostration. At the base of the left lung in rheumatic pericarditis there will often be found an area of dullness and intensely tubular breath sounds, the true nature of which must be recognized, as it may sometimes lead to a mistaken diagnosis of lobar pneumonia. Precordial pain, which is often regarded as a constant feature, is frequently absent in children.

Subcutaneous Nodules.—The appearance of subcutaneous nodules on the elbows, knees, malleoli, scalp, and spines of the scapulae is usually regarded as pathognomonic of the rheumatic infection, but it must be remembered that they can also be found in rheumatoid arthritis. Histologically they are roughly similar to the Aschoff nodes in the heart muscle and as a rule indicate a severe infection with severe cardiac involvement. The possibility of their persistence after all other signs of activity have disappeared seems unlikely.

Skin Manifestations.—The characteristic rash in rheumatism is erythema marginatum. It is a ringed eruption changing daily in outline, with very slightly raised margins and clear centres, and is seen mainly on the trunk and thighs. Once it has appeared it is likely to persist off and on throughout the active phase and even after all other signs of activity have disappeared. It does not signify a severe attack; indeed, one's impression is just the opposite. Erythema nodosum should not be looked upon as evidence of rheumatism. This skin lesion may appear as an allergic phenomenon in association with various infections, notably streptococcal, meningococcal, and tuberculous. When erythema nodosum is associated with rheumatism it can be regarded as evidence of the streptococcal infection rather than of rheumatism. With rare exceptions the remaining cases will be due to primary tuberculosis and should be regarded as such until proved otherwise. It should also be remembered that a rash indistinguishable from erythema nodosum may also result from the administration of sulphathiazole, probably as a result of sensitization to the drug.

Chorea.—This deserves special mention, because of all the manifestations of rheumatism it is the one most likely to occur alone and is least likely to lead to serious heart lesions. The subject, usually female, may have several attacks of chorea without apparent damage to the heart, and indeed without any other signs of rheumatism. Nevertheless all chorea should be regarded as rheumatic in aetiology. Habit spasm, in which the same movement is repeated over and over again, is readily confused with chorea and its differentiation is often a matter of great difficulty.

Differential Diagnosis

The diagnosis of acute rheumatism must be made on the history and clinical findings alone; in some subacute cases it may be necessary to delay making a definite diagnosis until the early course of the disease can be observed.

Abdominal pain during the early and acute phase of the rheumatic process may arouse suspicion of an acute abdominal condition, or an acutely tender and swollen joint may be confused with haematogenous osteitis, but in each case the history and a careful physical examination of the patient should serve to establish the diagnosis.

Anaphylactoid purpura (Henoch–Schönlein type) with its joint involvement bears a superficial resemblance to rheumatism. It is a form of primary purpura and is characterized by other manifestations such as abdominal pain, haematuria, and, of course, purpura, which should serve to distinguish it from rheumatism. The heart is not affected in anaphylactoid purpura.

Rheumatoid arthritis (Still's disease) may have an onset indistinguishable from that of rheumatism. Although they have many signs in common (arthritis, nodules, pericarditis), the course and prognosis are quite different. In rheumatoid arthritis the lesions tend to be symmetrical and the smaller joints, especially the interphalangeal ones, are more often affected so that the fingers are swollen at the base and taper towards the tip. The arthritis is not relieved by salicylates in the same way as it is in rheumatism, although it is customary for some improvement to occur. Splenomegaly and enlarged lymph nodes are found in about one-third of the cases. Furthermore, rheumatoid arthritis does not seem to be associated with infection by the Group A beta-haemolytic streptococcus as is rheumatism.

Also polyarteritis nodosa, disseminated lupus erythematosus, and occasionally subacute bacterial endocarditis may at times simulate rheumatism when heart and joint involvement are associated with pyrexia.

Treatment

Modern hormone therapy notwithstanding, salicylate, either as the sodium salt or as acetylsalicylic acid, remains the safest and most satisfactory drug in the routine treatment of rheumatism. In a recently published controlled study of the value of cortisone, A.C.T.H., and aspirin* no evidence was obtained that any of the three agents resulted in a termination of the disease, and some of the patients in each group developed fresh manifestations during the period of treatment. In the acute fulminating case and in pericarditis, however, the use of cortisone or A.C.T.H. is indicated and indeed may be life-saving. Such treatment should be carried out only under strict supervision and preferably in hospital. "Rebound" phenomena are likely to occur and may prove as difficult to control as the original manifestations, and for these salicylate will be found more valuable than the hormones.

There is no generally accepted dosage of salicylates: 1 gr. per lb. (0.14 g. per kg.) of body weight a day has been suggested, but some subjects tolerate the drug poorly and caution is required. To a child of 6 to 8 years 10 gr. (0.65 g.) of sodium salicylate and an equal amount of sodium bicarbonate every four hours would be a moderate dosage. The alkali diminishes the risk of salicylate poisoning by increasing its rate of excretion. It can be argued that smaller doses might be given without alkali. This is true, and if high blood levels of salicylate (40 mg. per 100 ml.) are desired the alkali may be omitted, but blood estimations should be carried out. Such a procedure is suitable only in hospital.

Salicylate poisoning is not uncommon. Vomiting is an early sign, although some authorities put this down to "gastric irritation," which is said to be relieved by the addition of the alkali. Tinnitus as a warning sign of intolerance or excessive dosage is valuable but is often, especially in children, either absent or unrecognized. Later, headache, hyperpnoea, and mental confusion may occur. The hyperpnoea results from the direct action of the salicylate on the centres in the medulla and is said to lead to a respiratory alkalosis. If this occurs the salicylate should of course be omitted and sodium bicarbonate given to increase the rate of excretion of the drug. For safety, it is sufficient to recommend the omission of one or two doses of the medicine if vomiting is troublesome or if there is any increase in the respiratory rate. Some children appear to tolerate acetylsalicylic acid better than sodium salicylate, and in such cases a change should be made. The dosage is approximately the same as for salicylate with alkali—namely, 10 gr. (0.65 g.) four times a day for the 6–8-year-old child and progressively larger doses as age advances. Alkali of course cannot be added. Calcium aspirin is pleasanter to take and is more soluble, but is expensive.

Modern conceptions of the aetiology of rheumatism suggest that at the onset of an attack a throat swab should be cultured for the presence of specific streptococci, and if found a five-day course of penicillin should be given. Tonsillectomy merely because the patient is a rheumatic subject cannot be justified. Relapses occur in tonsillectomized children as often as in non-tonsillectomized children.

British Medical Journal, 1955, **1**, 555.

General Care

Nothing so far has been said about the general care and rest in bed. These are important. The duration of rest in bed for the average case is about 8 to 12 weeks, during the first four of which salicylate is given in diminishing doses. Often, however, relapses occur and the period of rest must be correspondingly lengthened. The sedimentation rate, the sleeping pulse rate, the size of the heart, and the general well-being of the patient must all be considered in assessing the amount of bed rest necessary. The convalescence will be long, with gradually increasing activity over several months. Even late in convalescence strenuous exercise causing undue fatigue should not be allowed. Hard-and-fast rules cannot be laid down and each case must be considered on its merits. On the other hand, one must avoid creating an atmosphere of invalidism, which in the long run may produce in children serious psychological problems. Residual murmurs in patients seen by the doctor for the first time need very careful consideration, and in those unfortunate subjects in whom there is severe and permanent damage to both mitral and aortic valves the decision to confine the patient to bed should not be lightly taken.

Prevention

Recent work has indicated that by the prevention of streptococcal throat infections over long periods the number of relapses and recurrences can be greatly reduced. Short courses of aspirin every two to three months were tried, but the results were not striking. The use of one of the sulphonamides in doses of 0.5 g. once or twice daily has been more successful, and the results obtained during the last war in the United States Navy were impressive. Because this form of therapy is not entirely without danger it has been replaced by penicillin: a daily oral dose of 300,000 units, given under fasting conditions to ensure absorption, has been recommended. Whether this form of prevention should be used in every case of rheumatism is arguable. Many subjects have only one attack of rheumatism (monocyclic) and in them prophylaxis may not be necessary, but in those with frequent attacks (polycyclic) and in those in whom the mischief seems to smoulder its use is probably justified. The duration of the prophylactic treatment has not yet been determined, but in view of the seasonal incidence of streptococcal infection and rheumatism it should be given during the late winter and spring months for several years if it is to be effective. Recurrences are most frequent within five years of the initial attack. The only other method of prevention is for the subject to live in an area where streptococcal infections are seldom encountered, a measure that is seldom practical.

Prognosis

Generalizations about the prognosis are not very helpful when it comes to assessing the individual case: there are too many variables. The prognosis is dependent on the degree of damage to the heart, which may not be apparent for years after the rheumatic process is apparently at an end. There are in fact two waves of mortality; the first is at its height during the first two years after the initial infection, gradually disappearing during the next three years. These early fatalities result from the overwhelming nature of the rheumatic infection. The second wave occurs in adult life, when the late effects of the rheumatic process cause serious valvular damage.

It has been estimated that 50% of patients recover from their initial attack without apparent heart damage, but 50% of these will show signs of rheumatic heart disease in later life.

Next article on Emergencies in General Practice.—"The Acute Abdomen" (Part I), by Mr. R. Milnes Walker.

BRITISH ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

[FROM A SPECIAL CORRESPONDENT]

A preliminary report of the 117th annual meeting of the British Association, held at Bristol from August 31 to September 7, was given in last week's *Journal* (p. 672). The following account, dealing with other contributions of medical interest, is in continuation of that report.

Genetics and Medicine

A discussion on genetics and medicine, held jointly by the sections of zoology, physiology, and psychology, was introduced by Dr. HANS GRÜNEBERG (reader in genetics, London University). A few months ago the Medical Research Council had set up a group to study the pathology of inherited diseases in animals, the object being to throw more light on the part played by hereditary factors, or inborn constitution, in human disease. Many close counterparts of human anomalies, such as spina bifida, anencephaly, hydrocephaly, hare lip, cleft palate, continued Dr. Grüneberg, had been encountered in laboratory animals, particularly the mouse. Once the anomaly had been noted, it was generally possible to produce a stock in which it was present either in all animals or in a predictable proportion. In the case of hare lip and cleft palate the obvious interpretation was that the frontal and maxillary processes had failed to fuse. But when a similar condition in the mouse became available for embryological study it was soon clear that in some embryos the processes fused, but later became separated again. This had been suspected, admittedly, in some cases of human hare lip, but there was a difference between knowledge and suspicion. A second example was congenital hydrocephalus in the mouse: an obstruction to the pathway of the cerebrospinal fluid in the brain was here part of a general skeletal anomaly, of which the first effect was a general reduction in the size of all membranous skeletal structures as they were formed. As an example of an inherited disability which tended to develop in early or middle life, Dr. Grüneberg instanced deafness. During the last year it had been discovered that several distinct kinds of deafness occurred in laboratory mice; they could be studied on completely fresh material and before the stage of clinical deafness. Nothing had been known about them until they were systematically searched for; then they were immediately discovered. Other possible fields of research were on resistance or susceptibility to various infectious diseases which, from the very few critical data, were thought to be partly under genetic control.

In the same session Dr. J. A. FRASER ROBERTS (director, Burden Mental Research Department, Bristol) described the use of family studies in research on the aetiology of mental deficiency. Very little of the sum total of mental deficiency depended on single gene differences, he said, although some modest proportion of severe defect, idiocy, and imbecility, in addition to some rare special types, depended on recessive genes. The great bulk of cases represented a heterogeneous assembly of imperfectly developed or damaged central nervous systems, and for this mass hopes of genetic analysis could only be modest.

Dr. ELIOT SLATER (Genetics Unit, Institute of Psychiatry, University of London) gave a provisional report of an investigation, in collaboration with Mr. JAMES SHIELDS, of 62 pairs of twins, of whom one at least in each pair had had a neurotic illness. Of the uniovular pairs studied 53% had concordant histories—compared with a figure of 25% in binovular twins—indicating that hereditary constitution played some part in causation. However, he placed the main emphasis on environmental causes of breakdown. These were mostly intelligible at a common-sense level; they included relationships with parents and spouse, occupational and psychological stresses, and physical health.

Sensory Pathways

In his presidential address to the section of physiology on "The Sensory Pathway," Dr. R. S. CREED (New College, Oxford) contrasted the degrees of summation effected respectively in sensory messages "from the two great paired sense-organs of sight and hearing." In the case of the eyes, binocular brightness was only slightly greater than uniocular, and binocular fusion was a fusion of percepts rather than a result of confluence of physiological pathways; but with the ears summation was almost perfect. That summation might not take place until the cortex was reached was suggested by the summation of clicks sounded not quite simultaneously in the two ears, with localization on the side of the first click. The fact that a time difference as small as two ten-thousandths of a second was enough to allow localization implied the retention of time relations between nerve impulses to this degree of accuracy after relay through several synapses, which seemed to him remarkable. Dr. G. GORDON (Brasenose College, Oxford) referred to experiments to discover whether the different patterns of response in the fibres of a peripheral nerve when different stimuli were applied to the skin were in any way paralleled higher up in the nervous system. Cells had been found in the central system which seemed to respond only when hairs were moved on the surface of the skin, and the central, like the peripheral, pathway was a fast one. Dr. I. C. WHITFIELD (Department of Physiology, Birmingham University), in a paper on the nervous mechanism of hearing, said that the function of the nervous pathway between the ears and the higher brain centres was the gradual transformation of the response into one capable of being utilized by other parts of the nervous system. The analogy was not with a telephone cable containing repeaters, but rather with the devices in the British–European television links, which converted a picture produced by cameras working on one system into a picture capable of being utilized by receivers working on another system.

Nucleic Acids and Chromosomes

The discussion on the nucleic acids which was introduced in the section of chemistry by Sir ALEXANDER TODD, F.R.S., as reported last week, was supplemented by another, held jointly by the sections of physics, zoology, and botany. This dealt mainly with deoxyribonucleic acid (D.N.A.). Biological and biochemical introductions by Professor J. B. S. HALDANE, F.R.S. (University College, London), and Professor J. N. DAVIDSON (Glasgow University) were followed by a summary of evidence of structure by Dr. M. H. F. WILKINS (Medical Research Council Biophysics Research Unit, King's College, London). How D.N.A. controlled the development of hereditary characteristics was a mystery to which the interaction of proteins and D.N.A. might provide the key. The way in which D.N.A. was bound in sperm heads to protamine had recently been determined, and the structure of the more complex nucleohistone was being studied; its characteristic organization consisted of crystallites containing many D.N.A. molecules, with a considerable space filled by water. The water component of the crystallites might be associated with their biological activity, enabling specific and growth-controlling substances to diffuse into the cell as a whole. In spite of simplicities found in these structures, chemical and physical studies of chromosomes had only begun, and time would be needed before a biophysical picture of genetic mechanisms would emerge. Dr. F. H. C. CRICK (Medical Research Council Unit, Cavendish Laboratory, Cambridge) sketched persuasively the theory of the self-replication of D.N.A. which, with J. D. WATSON, he had put forward.[1]

Psychology of Blushing

The section of psychology ranged widely in its programme. Besides taking part with other sections in the session on

[1] *Nature*, 1953, **171**, 964.

genetics and medicine (see above) and in another on cerebral activity (with the section of physiology), it discussed the work of psychologists in industry, child guidance clinics, approved schools, and prisons; the contribution of psychoanalysis to the understanding of human behaviour; aspects of education, such as the value of co-education and the educational implications of left-handedness; and the social effects of rehousing. In a discussion on language, Sir RUSSELL BRAIN, P.R.C.P., spoke on the semantic aspects of aphasia. Dr. J. SANDLER described a study at the Tavistock Clinic, by himself and Mr. V. RAKOFF, of the personality traits of those who blush easily. Their main conclusion, based on an analysis of replies to an elaborate questionary, was that the overriding emotion experienced by blushers is one of shame. The fact that it was shame rather than guilt suggested that the blusher's conscience in early childhood took the form of "I must not be seen to be bad" rather than "I must not be bad." Blushers, they concluded, might be unconsciously afraid that their early sexual activities were "written all over their faces."

SECOND INTERNATIONAL CONGRESS OF NEUROPATHOLOGY

OPENING CEREMONY

The Second International Congress of Neuropathology was opened on Monday morning, September 12, at the Royal College of Surgeons in London. The president, Dr. J. G. GREENFIELD, who took over from the president of the First Congress, Dr. MARIO GOZZANO (Rome), welcomed the members, about 400 of whom had already been enrolled, and said that he hoped the Congress would result in a great stimulus to research in neuropathology. The programme, which extended until September 17, was a formidable one, comprising some 180 papers. A display of scientific exhibits had been arranged at the Royal College, and there were also an exhibition and demonstrations at the Maudsley Hospital.

After Dr. IVAN BERTRAND (Paris), speaking in French, had proposed a vote of thanks to Dr. Gozzano for his presidency of the First Congress, and Dr. W. SCHOLZ (Munich), speaking in German, had seconded, Dr. GREENFIELD introduced Sir Henry Dale, O.M., F.R.S., who in a few words opened the proceedings. Sir HENRY DALE said that the president had introduced him as one whose name would be familiar to most of them, but he really could make no pretension to mastery of this relatively new subject of neuropathology or to have taken any part in contributing to the growing body of scientific knowledge which it now incorporated. The programme bade fair to initiate some stimulating controversies during the week, and he congratulated in advance those who had taken part in what must have been a heavy task of organization. They had been eager to show those who came from other countries that their British colleagues could do well at this organizational task, and he was sure that London would rise to the occasion.

The Scientific Spirit Among Nations

Sir Henry went on to speak of the genuinely international nature of the Congress. It was international not only in name and intention but by the truly inclusive nature of its membership and the sources of its papers. Apart from the home contingent of British members and those from the overseas Dominions, there were members present from thirty other nations, representing every kind of race, political creed, and loyalty, but all of them united in a common aim and interest, and meeting in a spirit of good fellowship. He trusted that the Congress, innocent as it was of political intention, and seeking only the advancement of science and knowledge for its own sake, would do something for better understanding among nations, and be another sign of the revival of the scientific spirit and enterprise on the international plane of which recently there had been some welcome examples. He had had only a hasty glance at the richly varied programme, but it was evident from the titles of the papers how the study of the pathology of the central nervous system was dependent on the close co-operation of the neuropathologist and the clinical student of human disease.

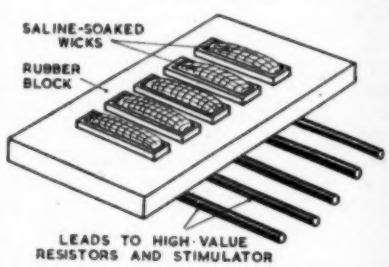
He noted also the many papers which dealt with the new techniques of investigation—encephalography, angiography, radioactive isotopes, and phase-contrast microscopy—and that a joint session was to be held with the 4th Symposium Neuroradiologicum, which was meeting in London at the same time (see p. 745).

Representatives of the various countries (in most cases the chairmen of the National Committees on Neuropathology) were then introduced to Sir Henry Dale; they included Dr. N. I. GRASCHENKOFF, of the Academy of Sciences, Moscow. A vote of thanks to Sir Henry Dale was proposed by Dr. ARMANDO FERRARO (New York) and seconded by Dr. G. LAFORA (Madrid). The Congress then immediately embarked upon the work of the first of the 16 scientific sessions, which occupied it for the ensuing four days.

Preparations and Appliances

THE "MULTIWICK" ELECTRODE FOR NERVE STIMULATION

Dr. WILLIAM W. MAPLESON, B.Sc., Ph.D., of the Department of Anaesthetics, Welsh National School of Medicine, Cardiff, writes: It is often difficult to maintain constant over long periods the muscular contractions produced by stimulating a motor nerve submaximally by means of an electrode placed on the skin. An electrode has been designed which appears to be a considerable advance in this direction. It consists essentially of a number of saline-soaked wicks mounted together in a rubber block, but separately connected through high-value resistors to the output of a constant-current stimulator. This ensures that an equal current flows through each wick, to merge into a large volume of nearly constant current density around the nerve to be stimulated. Thus small movements of the electrode relative to the nerve do not materially affect the intensity of current to which the nerve is subjected.



This "multiwick" electrode is a marked improvement over simple stimulating electrodes of the same size or larger. The reason for this is believed to be that with a large single electrode most of the current flows through a relatively small portion of its surface area and so tends to produce a narrow "pencil" of current within the tissues.

The pattern here illustrated has five wicks and has been used for stimulating the median nerve at the wrist to produce contractions of the short muscles of the thumb. No doubt the principle could be adapted for stimulating motor nerves elsewhere in the body. A full description, together with suggestions for developments, has appeared elsewhere.[1]

REFERENCE

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Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Time for Research

SIR,—Dr. Douglas Gairdner's letter (*Journal*, August 27, p. 561) was naturally of great interest to me. It deals with the shortage of doctors willing and qualified to devote time to research. He says, "What is first needed is a change in the climate of opinion within the profession towards this matter." I think he is quite right; but a change in the administration of the Health Service is also necessary if we are to overcome the difficulty defined by Dr. Gairdner when he says that few young doctors "dare to take the risk of leaving what they judge to be the accepted ladder leading either to general practice or to consultancy." In my specialty if the young man is to engage in research likely to be of any value he must be relatively senior—that is, about first-year senior registrar—and he must pursue his research for not less than two years. University research fellows are rarely paid more than half the salary of a senior registrar. However keen a man may be and however suitable to research, it is clearly unreasonable to expect him to take a step which not only causes a very substantial drop in salary but also prejudices his prospect of obtaining a consultant post.

It therefore seems to me that, in addition to a change in opinion among the people responsible for making appointments, there must be an agreement that research students shall retain the salary and status they have attained in the National Health Service. It might be that the best way to do this would be to combine clinical and scientific responsibilities. Such an arrangement needs not merely the approval but also the encouragement of the Minister of Health.—I am, etc.,

Liverpool, 7. BRYAN MCFARLAND.

Acute Pulmonary Oedema

SIR,—I should like to thank Dr. Graham W. Hayward for his interesting article on acute pulmonary oedema (*Journal*, June 4, p. 1361). It would seem that the Welch hypothesis, for primary cardiac lesions at any rate, is amply confirmed. For many years I have been a strong supporter of the view that the "terminal pneumonia" complicating neurological lesions, such as head injuries or acute trauma to the cervical cord, is, in essence, acute pulmonary oedema. It is some satisfaction to see this view being generally approved. The inhalation of nasal discharges, etc., may well be an aggravating factor in head injuries, but the clinical evidence points strongly to acute pulmonary oedema as the basic lesion. In many instances the recovery of function following severe trauma to the central nervous system is remarkable indeed; but the all-important factor appears to be time. Thus a study of the mode of dying could be as profitable as that of the primary cause of death.

Dr. Hayward's paper provides a further stimulus to associate acute pulmonary oedema of primary cardiac origin with that of neurogenic origin. In my experience the pulmonary oedema of the latter is not nearly so acute in onset, nor is any cardiac irregularity clinically obvious. However, as I see it, a study of the literature leaves little doubt that, under certain conditions, interference with parts of the nervous system can lead to incoordination of ventricular action and pulmonary oedema.

A survey of the clinical, pharmacological, and experimental evidence up to 1943 led me to the view that the heart's action was influenced to some extent through autonomic reflex arcs, and that part of the role played by the central centres of autonomic function was that of a control similar to the upper motor neurone of the somatic system. This would conform to the general law of release of function in the nervous system. Experimental physiology indicates that the sino-aortic nerves normally exert a tonic (afferent) inhibitory effect on the cardiac sympathetic and thus help to maintain the normal cardiac rhythm.[1] More recent work[2] has provided evidence for the existence of spinal reflex arcs for the vascular system.

I make no pretence at explaining these views on an anatomical basis, as, to me, the present concept of the autonomic system is controversial and the terminology open to question in some of its physiological implications. To a clinician, a study of functional results is more important. Thus there is evidence that an antagonism exists between the central and peripheral parts of the sympathetic nervous system,[3,4] and that overaction of the sympathetic at the periphery can produce pulmonary oedema.[1,5] The experimental work of Cameron and De[6] is of great interest, though I think their findings could be better interpreted along the lines of sympathetic release.

Theorizing on the basis that autonomic reflex arcs and overaction of the sympathetic at the periphery can produce pulmonary oedema, it can be seen that perverted cardiac control might arise in at least three ways: (*a*) stimulation of the sympathetic at the periphery (adrenaline); (*b*) augmentation of the afferent impulses through the reflex arc (tertiary ammonium anticholinesterases—for example, eserine); (*c*) elimination of the normal inhibitor to the reflex arc (lesions in the C.N.S.).

It has recently been suggested that the neurogenic pulmonary oedema complicating head injuries is due to an abrupt and massive rise in systemic vasoconstriction.[7] There can be no doubt that systemic hypertension is a frequent accompaniment of head injuries, but it is not my experience that it is invariable. In dislocation of the cervical spine with loss of cord conductivity, pulmonary oedema is delayed in onset and quietly progressive. In such cases I have not observed any significant rise in the systemic blood pressure. Furthermore, in experimental physiology it would appear that the pulmonary oedema resulting from section of the sino-aortic nerves is abolished by section of the cardiac sympathetic. The systemic hypertension associated with head injuries may well be another release phenomenon, and it seems more likely that it is a concomitant feature rather than the cause of pulmonary oedema. There can be little doubt that the work of the heart is enormously increased in these cases and particularly so when associated with hyperthermia.

After careful consideration of the evidence it seems justifiable to treat neurogenic pulmonary oedema by inhibiting the sympathetic at the periphery. Injection of ergotamine tartrate produced a dramatic improvement in a case under my care, with a clinically normal chest in a few hours. Death occurred at a later date from hyperthermia.—I am, etc.,

London, W.1. J. S. CALLCUTT.

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Position for Delivery

SIR,—I have not been able to consult as many textbooks as I should like, but so far as I can make out from them and inquiries in knowledgeable quarters it is still taught—or at least practised—that a woman should be delivered in the lithotomy or fully flexed thigh-on-abdomen position. Certainly when we recently opened our long-desired G.P. maternity block the delivery table had wonderfully padded supports for holding the woman's legs firmly so.

The purpose of this letter is to inquire whether it is not time for obstetricians to recognize that this is all wrong. The position has considerable advantages from the accoucheur's point of view, and personally I think the left lateral much better than the dorsal. It may also have advantages in the earlier stages of labour, but when it comes to delivering the head is it not incontestable that flexing of the thighs pulls the perineum forward and so tightens and narrows the orifice? This results in delay at the outlet, often necessitating the use of forceps and an episiotomy. I know that the thighs are also often abducted as well or flexed in an effort to provide more room, but this does not overcome the inherent obstacle produced by the flexion itself. It is said that the customer is always right, and most doctors will have had experience of the difficulty in getting an unanaesthetized, and particularly a partially anaesthetized,

woman to keep her legs flexed at the moment of delivery. Left to herself, she will always straighten them out and separate them widely.

This is, in fact, the way to provide the greatest relaxation of the perineum and so ease the delivery of the head. It took me nearly thirty years to realize these simple facts, and in the succeeding ten I have proved time and time again how right Nature is and how wrong is so much obstetric practice. The greatest difficulty is to get nurses to let the legs extend properly, and sometimes to hyperextend, as in the old-fashioned Walcher position. But when it is done the ease of delivery is often astonishing. Labour is hard enough without obstetricians and nurses putting unnecessary strains on the perineum that may lead to permanent weakness later on.

It is often forgotten how easy it is to overstrain ligaments under anaesthesia, and much backache after labour is not due to internal derangements but to overflexion under the anaesthetic. In the same way, I fear, many women go into hospital to have a dilatation and curettage for backache due to some gynaecological condition, and come out with one due to over-zealous production of the lithotomy position. In fact, the way patients' backs are often treated under anaesthetic—whether overflexed, or hyperextended, or no provision made to support the lumbar curve—horrifies me, and I hope this statement of elementary anatomical facts may do something to change the ordinary run of obstetric (and gynaecological and surgical) practice and reduce the toll of suffering due to traditional or thoughtless teaching.—I am, etc.,

Winsford, Cheshire. W. N. LEAK.

Dosage of Local Analgesics

SIR,—The letter from Dr. John Gordon (*Journal*, August 20, p. 489) describing the toxic effects due to the use of 60 to 70 ml. of 2% lignocaine for a forceps delivery is a timely one, as it would be unfortunate if either the increasing use of local analgesia for instrumental delivery or the reputation of a valuable new drug were to be prejudiced. The introduction of lignocaine has proved a revolution in local analgesia owing to the speed, certainty, and length of its action, and to its keeping and sterilizing properties. It must be looked upon as being more potent than procaine, however, as has been previously pointed out in correspondence in these columns,[1] and a 0.5% solution is adequate for pudendal block; and for more extensive infiltration, as for caesarean section, a 0.25% solution with adrenaline is satisfactory. The greater safety of weaker solutions for local analgesia is also well recognized, and Greenhill was unable to find any record up to 1946 of a death in obstetrics due to the use of 0.5% procaine. The volume of 1% lignocaine solution which Klink[3] found necessary to anaesthetize the whole perineum was only 10 ml. on each side if the injection was made close to the pudendal nerve. This technique requires considerable experience, however, and in practice a field block is usually carried out, but even then a total volume of much less than 60 to 70 ml. is sufficient.—I am, etc.,

Middlesbrough. BRYAN WILLIAMS.

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2 Greenhill, J. P., *Year Book of Obstetrics and Gynecology*, 1946, p. 159. Chicago.
3 Klink, E. W., *Obstet. Gynec.*, 1953, **1**, 137.

Comforters

SIR,—Your correspondent Dr. A. L. Cowan (*Journal*, August 20, p. 492) may be interested to know that orthodontists do not consider finger- or thumb-sucking is worth taking any steps to eliminate unless it persists after the age of 5 years. The preventive methods mentioned by Dr. Cowan are rarely successful, and, when they are, usually result in the development of an even less desirable habit—for example, nail-biting. If, however, the finger-sucking habit persists after the age of about 5 years it is very likely to produce dental deformities. The habit is quite easily cured by the fitting of a simple orthodontic plate, which provides the apparently necessary oral stimulation and is so designed as to correct any deformity which may have already developed. I am sure Dr. A. L. Cowan's problems will be solved if he will consult an orthodontist.—I am, etc.,

Wembley. J. H. AUST.

Amnesia after Swimming

SIR,—I can confirm from my own experience what Dr. J. W. Fleming reports in his interesting letter (*Journal*, August 27, p. 564). A few years ago, after swimming rather a long time, for me, in rather cold water in the Western Highlands, I had no memory of getting out of the water, returning to the house, or dressing. But I realized also that my mind had been filled with a coherent and vivid dream which repeated or was consequent upon a dream I had dreamt recently. The same thing happened this summer. I cannot now do more than float and swim a little on my back (partly as a form of physiotherapy for arthritis), but on one occasion I stayed in the water, quite comfortably warm, perhaps just a bit too long for me. After I had dressed and was resting I realized that I could not remember getting out of the water or dressing. And again my mind was filled with a coherent dream, which I recognized as a repetition of a recent normal dream.—I am, etc.,

Rushden, Herts. E. H. STRANGE.

Sudden Giddiness

SIR,—I was most disappointed on reading Dr. J. D. Spillane's article on sudden giddiness (*Journal*, September 3, p. 612) to find no mention of liver causation. I was at the time suffering from hepatic congestion due to the extreme heat and lack of exercise. This lasted for one week, with extreme giddiness on rising from a recumbent position, passing off in a few moments. There was highly coloured urine, faeces pale; no sickness or diarrhoea, but a feeling of nausea; no headache or deafness; no cerumen in ears.

After 49 busy years of general practice I have found this quite a common condition. In this time I have had only two cases of Ménière's disease. As to treatment, I have found mist. rhei ammon. c. sod. the most useful medicine, with, more recently, "veracolate" tablets, one or two at bedtime. I should like to know the pathology of this condition.—I am, etc.,

Sanderstead, Surrey. JOHN FINNEGAN.

Premenstrual Varicose Veins

SIR,—Mr. S. Rivlin (*Journal*, September 3, p. 618) is to be congratulated upon his recognition of the temporary exacerbation of symptoms and signs associated with varicose veins that may occur in the premenstrual phase of a woman's monthly cycle, but gynaecologists may be surprised at the explanation which he gives. His assumption that it is due to the increased venous return along the internal iliac veins, if true, would surely condemn every woman to the most extreme form of varicosities during the later months of every pregnancy when the blood supply to the uterus is so much increased. It is surely sufficient to invoke the customary explanation whereby the increased secretion of progesterone produces dilatation of veins in common with its action upon other smooth muscle.

It is perhaps of interest that patients will occasionally diagnose a pregnancy before the menstrual period has been missed by virtue of increased aching in their varicose veins.—I am, etc.,

Birmingham. W. G. MILLS.

SIR,—I first learned of the premenstrual aggravation of varicose veins from Mr. Noel Glover while a dresser in his varicose vein clinic at Guy's, but the explanation of it given by Mr. Stanley Rivlin (*Journal*, September 3, p. 618) is

certainly new to me. He implies that the venous return from the pelvis and leg respectively compete for entry into the common iliac vein and that "the increased premenstrual internal iliac venous return . . . cuts across and dams back that from the external iliac vein." Could sufficient pressure be built up in this way to cause the sapheno-femoral incompetence demonstrated by Mr. Rivlin? An alternative explanation (and the usual one, I believe) is that there is premenstrually a direct progesterone action upon the smooth muscle of the vein wall resulting in dilatation of the vein and valvular incompetence. This view would as well accord with the occurrence of varicose veins in early pregnancy as would the hydrodynamic theory above. It has the added advantage of invoking a mechanism already known to exist elsewhere in the body during pregnancy—namely, the smooth muscle relaxation which results in the development of hydro-ureter of pregnancy. There may be, of course, in addition mechanical factors responsible for the localization and asymmetry of the effect.—I am, etc.,

London, N.W.10. J. S. NORELL.

The Art of Dermatology

SIR,—The first two papers in your issue of August 20 are "The Art of Dermatology" by Dr. R. M. B. MacKenna (p. 449) and "The Whitfield Tradition of Therapy" by Dr. D. I. Williams (p. 453). When I was a medical student I consulted at different times both Dr. MacKenna and Dr. Whitfield on account of acne vulgaris. I obtained real help and sympathy from both these wise men, but they disagreed on the all-important question (let those scoff who have not suffered) whether blackheads should be extracted or left alone. It required only two months' trial, blackheads being extracted on one side of the face and not on the other, to prove the superiority, in the circumstances, of conservative treatment.

In the whole of therapeutics there is perhaps no easier opportunity for controlled experiment than in the local management of skin complaints. Why has it been so neglected?—I am, etc.,

"A GRATEFUL CRITIC."

Treatment of Tuberculosis

SIR,—It is 42 years since I was privileged to meet Osler, Robert Philip, Trevelyan, and Woodcock, of Leeds, at a luncheon to inaugurate the formation of the Yorkshire Tuberculosis Society. Leeds at that time was a great centre for controlling tuberculosis on a voluntary basis, and had a sanatorium at Gateforth, a tuberculosis hospital at Armley, and a dispensary in Great George Street, with a secretary and visiting nurse. At the meeting I found that Trevelyan was advocating the formation of a chest clinic at the Leeds General Infirmary. Unfortunately he died at an early age and his idea was not carried out.

Two years later the Bradford City Council initiated the first municipal anti-tuberculosis dispensary. Nurses and administrative staff were appointed and gradually the service was developed on lines approved by Philip, Vere Pearson, of Mundesley, and Jane Walker, who had the famous sanatorium for women. This was at a time when the local authorities were not required to have tuberculosis schemes. In those days pneumothorax was carried out "in carefully selected cases," and tuberculin testing "in all its forms" used as a routine. The services of the pathologist were extensively used, and later a private radiologist was employed in a part-time capacity. As each new idea came out it was carefully sifted, and if found suitable it was absorbed into the scheme, such as mass radiography and thoracic surgery.

During the second world war some of us were required for other duties, and on return to our posts found out that the scientists had discovered new methods of treatment. The whole scheme had to be carefully transferred from the local authority to a management committee. There was grave danger of losing beds so necessary for the care of advanced cases and the prevention of the spread of infection. B.C.G. had to be introduced somehow; much depended on the support of the local authorities. With regret I state that many carefully organized schemes were disintegrated. Now, however, things appear to have settled down somewhat. There is much to be said for the remarks of Dr. H. A. Crowther (*Journal*, August 27, p. 564) regarding a saner public health outlook. The modern chest physician has a wonderful opportunity of completing the wish of our great predecessor Robert Philip, and Sir George Newman, of the Ministry—the eradication of tuberculosis.—I am, etc.,

Bradford, Yorks. HAROLD VALLOW.

The Whitfield Tradition of Therapy

SIR,—Those who have acquired the art of opening the *British Medical Journal* must surely have felt themselves rewarded by reading Dr. David I. Williams's interesting and charming lecture (*Journal*, August 20, p. 453).

He regrets that "we have not yet educated people to know that scarcely any skin condition is contagious and that scarcely any skin condition is due to diet or lack of cleanliness." Surely the concern about contagion and hygiene is but a façade covering a deep-seated irrational horror of blemishes on the skin, comparable only to the universal horror of incest. For neither have the ladies invented a euphemism—each is too unspeakable. A skin disorder is always a "disease." Nothing will bring a mother to an infant welfare centre more certainly than spots on her child, spots that are often difficult to see, spots that she knows are neither contagious nor due to uncleanliness. The alacrity with which patients with skin disorders offer to pay their guineas for private consultations with dermatologists to avoid waiting two or three weeks and being seen in out-patient departments is striking. Patients' feelings about skin complaints are too intense and too deep for us to hope for results from education in the consulting-room or out-patient clinic. What, I wonder, is the psychological explanation of the psychologists' neglect of this field of investigation and study?

Finally, in contrast with Dr. D. I. Williams's original formula for Whitfield's ointment—namely:

Benzoic acid	...	25 gr. (1.6 g.) (5%)
Salicylic acid	...	15 gr. (1 g.) (3%)
Soft paraffin	...	120 minims (7.1 ml.) (25%)
Coconut oil	...	to 1 oz. (28 ml.)

Drs. J. E. M. Wigley and F. B. Fox, in "Favourite Prescriptions,"[1] gave the following original formula:

Benzoic acid	...	24 gr. (1.5 g.)
Salicylic acid	...	30 gr. (2 g.)
Coconut oil	...	120 gr. (8 g.)
Soft paraffin	...	to 1 oz. (31 g.)

Ignoring Dr. Williams's predilection for the measurement of soft paraffin in minims and Drs. Wigley and Fox's predilection for the measurement of coconut oil in grains, there still remain discrepancies too gross to be explained by accidental error. Please may we be told what Dr. Arthur Whitfield actually did prescribe?—I am, etc.,

Cheltenham. G. B. MATTHEWS.

REFERENCE

[1] Wigley, J. E. M., and Fox, F. B., *Practitioner*, 1950, **165**, 33.

Alcohol and Epilepsy

SIR,—In his letter relating to the subject of alcohol and epilepsy Dr. Milo Tyndel (*Journal*, August 6, p. 381) refers to the case of an epileptic patient described by Jewesbury,[1] in whom a fit had occurred "after drinking a good deal of beer the previous night." Whereas according to Jewesbury "the point of interest was that fluid retention seemed to increase [the patient's] liability to . . . fits," in Tyndel's opinion the more important factor in this case was that "it was not an indifferent fluid but an alcoholic beverage that was taken," and that "alcohol must be considered an even more potent precipitating factor [in epileptics] than large amounts of

fluids."[4] Tyndel also points out that "seizures following abuse of alcohol occur usually on the following day." Some of these points are illustrated by the case of a young epileptic out-patient of ours in whom fits used to occur regularly at week-ends, whereas he had no fits during the rest of the week. It occurred to the patient himself that there might be a connexion between his intake of alcohol and his fits. He did not drink during the rest of the week, but drank beer and spirits on Friday night and Saturday night: his fits usually occurred during day-time on Saturdays and Sundays. He gave up drinking alcohol last Christmas, and since then he has had no more than a total of two epileptic fits.

Among people who abuse alcohol habitually convulsions are not an infrequent phenomenon, though they are apparently not so common as they used to be. According to J. Ch. Smith[2] the tendency to convulsions in chronic alcoholics is specially strong with those who take stronger alcoholic drinks, particularly brandy (*Branntwein*), and he remarks that alcoholic convulsions practically disappeared (in Scandinavian countries) in 1917 when there was a considerable increase in the cost of alcoholic drinks. Among our own alcoholic patients, out of 110 males 25 (22.7%) stated that they had had convulsions in the past, which had taken place at an average age of 38 years. Five out of 50 female alcoholics (10%) gave a history of convulsions (average age: 43 years). The great majority of these patients had been heavy spirit-drinkers. "Withdrawal convulsions" occurring (in a very small proportion of patients) on the day after admission happened likewise in alcoholics who had been drinking spirits heavily over a long period; three of these were men, two women. This corresponds to the recent statement by the Expert Committee on Alcohol and Alcoholism[3] that, amongst other withdrawal symptoms, convulsions may occur in a proportion of drinkers "after a prolonged period of very heavy drinking" between the 24th and 48th hour after withdrawal. The Expert Committee on Alcohol[4] describes "characteristic E.E.G. changes" immediately after such convulsions, and Isbell *et al.*[5] obtained "a characteristic electroencephalographic pattern . . . during chronic intoxication with alcohol and during the withdrawal period." Among our own patients E.E.G.s taken usually a few days after the convulsions had occurred showed no abnormalities, and it is interesting to note that the only abnormal E.E.G. found amongst our alcoholic patients concerned a man who was later discovered to have a brain tumour.—I am, etc.,

Warlingham, Surrey. M. M. GLATT.

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1 Jewesbury, E. C. O., *British Medical Journal*, 1954, **2**, 1518.
2 Smith, J. Ch., in *Rauschgifte und Genussmittel*, 1951, edited by K. O. Møller, pp. 213 and 226. Basel.
3 "Alcohol and Alcoholism": Report of an Expert Committee, *Wld Hlth Org. techn. Rep. Ser.*, 1955, No. 94, p. 7.
4 First Report of the Expert Committee on Alcohol, *Wld Hlth Org. techn. Rep. Ser.*, 1954, No. 84, p. 7.
5 Isbell, H., Fraser, H. F., Wikler, A., Belleville, R. E., and Eisenman, A. J., *Quart. J. Stud. Alcohol*, 1955, **16**, 1.

Royal College of Midwives Appeal

SIR,—May I be permitted the use of your columns to call attention to the appeal that is being made to the nation on behalf of the Royal College of Midwives?

Briefly, the facts are that the present premises are quite inadequate for the purposes and needs of the College. Accordingly a very suitable corner site has been secured at 15, Mansfield Street, London, W.1, on which to erect an appropriate building. It is calculated that to acquire the site, to erect the building, and to maintain it on completion £150,000 is required. It is therefore hoped to raise this sum in the course of the appeal.

Apart from the many and increasing services contributed to British midwifery, the Royal College also serves world midwifery and undertakes the secretariat of the International Confederation of Midwives. A number of your readers will recall the first world congress of midwives which was held in London last year and was sponsored, organized, and financed by members of the Royal College and attended by representatives of 47 countries.

No doubt many of your readers will have a kindly sympathy for the good shape of the College, and indeed many will have personal contacts with its officers and offices, and may well feel disposed to support the appeal by sending a cheque, made payable to the "Royal College of Midwives Building Appeal," The Appeal Secretary, 57, Lower Belgrave Street, London, S.W.1.

Midwife members of the many branches of the College throughout the United Kingdom will in various ways be taking steps to raise funds for the benefit of the appeal, and the help and encouragement of your readers by co-operation with these social events would be most valuable and warmly appreciated.—I am, etc.,

London, S.W.1. C. S. B. WENTWORTH-STANLEY, Chairman, Appeal and Building Committee.

St. Luke's Day Service

SIR,—We should like, through the courtesy of your correspondence columns, to inform your readers of a special service for doctors which is to be held in October for the fourth year in succession in All Saints' Church, Langham Place, W.1 (by Broadcasting House). The date this year is two days before St. Luke's Day, Sunday, October 16, and the service will be at 11 a.m. Situated near the centre of the medical world, All Souls, Langham Place, like St. Peter's, Vere Street, which is now united to it, has often been styled "The Doctors' Church." Many who attended the services of the last three years have encouraged us to arrange another this year, and we hope that doctors will welcome this opportunity of attending a service of prayer and dedication at the beginning of the academic year. The President of the Association of Surgeons and the Chairman of the British Medical Association have kindly agreed to read the lessons. The preacher will again be the Rector.

Seats will be reserved for doctors and members of their family who apply for tickets in advance. Application (stating the number of tickets required) should be made to the Church Secretary, All Souls Vestry, Langham Place, W.1, by Thursday, October 13.—I am, etc.,

London, W.1. JOHN R. W. STOTT, Rector.

POINTS FROM LETTERS

Advertisements

Dr. D. J. PARRY (London, N.2) writes: I am astounded at the extent to which certain commercial drug firms advertise their products to newly qualified practitioners. Any firm is entitled to place before us details of its wares, and no doubt recently qualified practitioners receive especial attention, but to receive, within ten weeks, no less than fourteen separate notices relating to one brand of antibiotic seems to me to be excessive. Is advertising to this degree justified? I assume it must be profitable for it to occur, but their financial resources could surely be diverted through more useful channels and so avoid such a persistent succession of notices that amount almost to a nuisance.

Tax on Health

Dr. G. C. PETHER (Hitchin, Herts) writes: The window tax was regarded as a tax on health, and, in due course, abolished. Is it not a fact that one may carry out improvements to a house which will make it more healthy? And is it not true that such improvements may entail an increase in rateable value? Why do we condemn the first tax mentioned and approve the second?

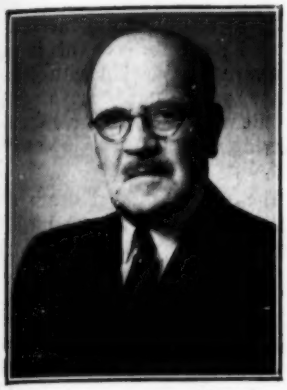
Book Reviews

Dr. B. J. BOUCHÉ (Boulia, Queensland, Australia) writes: The letter from Sir Heneage Ogilvie on "Book Reviews" (*Journal*, July 2, p. 58) is all one-sided. You did quite right in printing Dr. I. Galdston's letter (*Journal*, June 11, p. 1430). If a reviewer has not the plain courage of his convictions and takes shelter behind anonymity, then his opinion were better unexpressed. . . . If I ever go into print, as I hope one day to do, I would certainly like a reviewer to be frank but with courtesy, and I would like to know his name, etc.

Obituary

R. M. F. PICKEN, C.B.E., M.B., D.P.H.

We record with regret the sudden death at his home in Cardiff on September 7 of Provost Ralph M. F. Picken. He was 71 years of age, and was to have retired from the post of Provost of the Welsh National School of Medicine at the end of this month. Although apparently well, he himself was not unaware of some untoward symptoms, but in spite of these he continued his public services to the end, and on the day before his death spent the morning attending to the affairs of the medical school in his usual careful way.



[*Bassano*

Ralph Montgomery Fullarton Picken was born on July 25, 1884, the son of David Picken, a retired schoolmaster of Glasgow. His birthplace was Lamlash, in the Isle of Arran, which in his youth he knew well and where he enjoyed returning in after years. From the Glasgow High School and Allan Glen's School he went on to Glasgow University, where he graduated in pure science in 1905 and in medicine in 1908, taking third place in his year. In 1911 he took the Diploma in Public Health of Cambridge University. After graduating he served for two years successively as senior house-surgeon to Sir William Macewen in the Glasgow Western Infirmary, house-physician in the Royal Hospital for Sick Children, Glasgow, and resident obstetrical officer in the Glasgow Royal Maternity and Women's Hospital. In 1910 he entered the public health service as a resident assistant physician in Ruchill Fever Hospital, Glasgow, and in 1912 became acting medical officer for the county of Renfrewshire and medical officer of health of Port Glasgow. For one year he then held the post of assistant medical officer of health and school medical officer for the county of Dumfries and burghs before returning to the Glasgow public health department, where he remained until 1921, finally becoming divisional medical officer for one of the largest of the five administrative areas in the city.

In 1921 Picken was appointed medical officer of health for Cardiff, and he took a principal part in conceiving and promoting many new developments, among which may be mentioned a hospital for early rheumatic heart disease, public health laboratories, an orthopaedic scheme, immunization of children against diphtheria, and the inauguration of new special schools and classes for physically and mentally defective children. He was closely associated with the work of the Welsh National Memorial Association in the area. Particularly significant, in view of his future destiny, was the erection of the large general hospital at Llandough, at first planned for the Cardiff Board of Guardians and in 1930 appropriated by the city; Llandough later became one of the clinical institutions of the Welsh National School of Medicine. While medical officer of health he was a lecturer in public health, and when, in 1933, he was appointed Mansel Talbot Professor of Preventive Medicine he began to bring his influence as a teacher and administrator upon the Welsh National School of Medicine. He became the second provost, succeeding Professor A. W. Sheen in 1947. He retired from the chair of preventive medicine in 1949, but continued as Provost until his death.

Although during the later part of his career Picken had to devote much of his time to teaching and administration, he had behind him a record of useful epidemiological research. He had written on measles, typhoid fever, and "some unusual forms of nervous disease" during his days in the Scottish public health service. From 1940 to 1946 he wrote on subjects connected with public health and preventive medicine in the *Medical Annual*, and for some years he contributed articles on public health law to *Local Government Law and Administration*.

During his long and active public life Picken filled many positions of trust and influence in the profession. He was a member of the General Medical Council, vice-chairman of the Welsh Regional Hospital Board, and chairman of the establishment committee of the board of governors of the United Cardiff Hospitals. He had also held at different times the offices of president of the Society of Medical Officers of Health and of the Welsh branch of the society, president of the Cardiff Medical Society, and for many years had been a member of the General Nursing Council. He was an enthusiastic member of the British Medical Association, and at various times between the years 1929 and 1945 he served on nearly fifty committees and subcommittees. Chief among these were the Public Health Committee, of which he was chairman from 1932 to 1945, the Medico-political Committee, the Advisory Committee on the Salaries of Whole-time Public Health Medical Officers, the Insurance Acts Committee, the Central Medical War Committee, the Hospitals Committee, the Medical Planning Commission, and the Standing Joint Committee of the B.M.A. and the T.U.C. He was also a member of the Council from 1930 to 1945, when he felt obliged to give up his B.M.A. work on assuming the duties of Provost of the Welsh National School of Medicine. In 1942 he acted as chairman of the Council during the absence of Mr. H. S. (now Sir Henry) Souttar in India. The Association was fortunate enough to regain his services as a member of the arrangements committee in connexion with the Cardiff Annual Meeting of 1953. He was president of the Section of Public Health when the Association held its Annual Meeting at Cardiff in 1928 and a vice-president of the same Section at the Centenary Meeting in 1932. He was also chairman of the Cardiff Division in 1939. When the B.M.A. held its Annual Meeting at Cambridge in 1948 he was elected a Vice-President in recognition of his exceptional services to the Association. In the following year he was appointed C.B.E.

In 1935 Picken visited public health centres in the United States as the representative of Great Britain on a study tour promoted by the Health Organization of the League of Nations, and became a close friend of many leaders in the public health field in that country. Before and during the war he was a particularly valuable member of the Young Practitioners Committee and the Central Medical War Committee, and was vice-chairman of the Medical Personnel Priority Committee: in these positions the decisions he had to take were often hard, but were always known to be just. He was a member

of the Nuffield Provincial Hospitals Trust, and his established position in the world of both social and academic medicine fitted him to be one of those chosen to carry out the hospital survey throughout Great Britain between 1943 and 1945. The report on the South Wales hospitals, for which he was largely responsible, showed that his stringent attention to detail and his precise accuracy of observation were completely compatible with a broadness of outlook on the problems confronting a new health service, and in particular he stressed the need for the close association between hospitals and universities which is a feature of the National Health Service Act.

Like many other Scotsmen who have settled in Wales, he gave his best to the country of his adoption, and from the beginning took his place as one of the leaders in Welsh medicine. His triple responsibility as Provost of the school, vice-chairman of the regional hospital board, and member of the board of governors of the teaching hospitals gave him the opportunity to use his influence to bring these three bodies into an unusually harmonious concord. He had an important part to play in the affairs of the University of Wales, and his acceptance in these circles is an indication at once of his own merit and the discernment of his academic colleagues. His care in guiding the school of medicine through the difficult post-war years will ever be remembered by his colleagues and by the students. The proposal for the new teaching centre in Cardiff was one into which he threw all his energies, and as chairman of a working party he produced a most detailed schedule of the accommodation required, which is now being considered by the appropriate authorities and is a model of its kind in clarity and directness. His death removes from Wales one who would have rejoiced to see the completion of this project and for whom there would be no memorial more suitable.

Although of late years he had little time for secular activities he found congenial fellowship among a select circle of friends, who shared his artistic and musical inclinations. He is survived by his widow—formerly Miss Jean Brand Watt, whom he married in 1913—his son, Dr. David Picken, and his two daughters, to all of whom we extend our sympathy.

We are indebted to Sir WILSON JAMESON for the following appreciation: The death of R. M. F. Picken has robbed public health of another outstanding personality. He studied medicine in Glasgow at a vintage period, when such characters as "James Bridie" were undergraduates. I met some of them in my young days at inter-university conferences. These times left an indelible mark on Picken, and many a story he had to tell of them. I did not get to know him until he became medical officer of health of Cardiff—and what a success he made of that. He threw himself into the work of the Society of Medical Officers of Health, helped to edit their journal, became their president, and represented them with great ability and acceptance on various B.M.A. committees. He was appointed to the Welsh chair of preventive medicine shortly after I went to the London School of Hygiene and Tropical Medicine, and we soon found many ways in which we could work together. He was a first-class teacher and a patient and generous examiner. He made his department a real force in the Cardiff Medical School, and interested himself in the training of health visitors and, indeed, of nurses generally, for he was at one time a member of the General Nursing Council. Both his daughters are State-registered nurses. He was obviously the right man to make Provost of the Medical School when that appointment fell vacant, and he undertook his new duties with his usual enthusiasm and ability. When the National Health Service was introduced Wales was fortunate in having Picken both on the regional hospital board and on the board of governors—these two bodies owe much to his guidance.

It is given to few men to have served so successfully in such a variety of fields. But he was a man of wide interests and culture. To spend some time as a guest in his home, as I frequently did, was a delightful experience. Latterly he had his whole family round him, and he sat like a patriarch offering advice and, what is much more important, listening sympathetically. He loved his pictures, a bottle of wine, and a good book. He was interested in people, and understood them, especially the young; no wonder he was a good administrator. He identified himself with Wales and knew the countryside well, through which he drove in his earlier days in what I thought was a hair-raising manner: to ride with Picken in his old Riley was something to remember. He was on the point of retiring from the provostship when he died suddenly. I really believe this is as he would have wished it. We sympathize deeply with Mrs. Picken, her two daughters, and her son in their bereavement, but it must be some comfort to them to know that all those who knew Picken will join in saying, "Well done, good and faithful servant."

Professor A. G. WATKINS writes: The sudden death of Provost Picken has cast a gloom over all concerned with the Welsh National School of Medicine. During his time as its Provost the medical school has developed after early difficult years into a flourishing institution, and to him must go the main credit. He was never happier than when drawing up a memorandum or abstracting a complex Government publication for the clarification of his colleagues. He was scrupulous in detail, almost to an obsession, and nothing left his pen that had not been carefully worded and corrected to the last comma. To a young medical school this was of great value, for it kept us straight in complicated administrative measures, but, more than that, he guided the school in its policies with a canny wisdom which will remain its foundation in years to come. As a chairman or member of a committee he was at his best, and his penetrating mind went straight to the heart of the problem. Whenever he spoke, his words were listened to with care, for they were constructive, and no one was better at summing up a discussion and pointing the way to future action. His manifest integrity gave him a position of authority. His leadership in the medical school and the hospitals of Wales will be sadly missed.

To those of us who came to him with our problems he gave sound advice, sometimes a little depressing to our egos, but its wisdom became obvious in time. In such ways was a deep respect engendered, and our sadness at his death is a token of real affection for him. He was at times a "dour Scot," and he suffered those whom he considered fools with little patience, but when their backs were turned he often took some unseen step to help, and many a medical student who quailed before his frown had reason to be grateful to him, though the last person to know what hidden hand had come to his rescue would be the student.

It was on the golf course that Picken most readily shed his protective mantle, and, though he had little time for golf in latter years, as a student in Glasgow he was a scratch player and no doubt took some beating. His general interests were wide; he loved pictures, and the presentation of his portrait on his impending retirement by his colleagues delighted him more than he showed. A man of character and distinction, we shall remember him with an affectionate respect, and his family, to whom we extend our deepest sympathy, can rest assured that his contribution to medical education in Wales will not be forgotten.

Dr. GEORGE F. BUCHAN writes: It was with much regret that I heard of the death of Ralph Picken. He was a lifelong friend. Ralph had a distinguished career at the University of Glasgow and entered the public health service well equipped for the many tasks he undertook. He left

his imprint on the health practices of Glasgow and Cardiff, and later, as professor of public health in the Welsh National School of Medicine, launched many aspirants to fame in the public health service—men and women imbued with a full knowledge of the principles they should observe in their daily work. I spent four weeks with him in Denmark some 30 years ago studying public health practice in that country. We were fortunate in having as our colleagues on that occasion public health workers from countries as far apart as the U.S.A. and the U.S.S.R. At that time Tom Parran, now dean of the School of Hygiene of the University at Pittsburg, was chief medical officer of the U.S. Public Health Service and was one of the party. As the three English-speaking members of the tour, we naturally were much together and became known to the others as "The Three Musketeers." We three have often talked over the experience we obtained from this visit, which turned out to be of great value, not only scientifically and practically, but also socially. Picken was a rare travelling companion, never upset by any contretemps and invariably helpful.

Ralph Picken was probably best known to the medical profession in Britain as chairman of the Public Health Committee of the B.M.A. He was also a member of the council of the Society of Medical Officers of Health for many years and president in 1944–5. When he first took the chair of the Public Health Committee of the B.M.A., the medical officer of health and the general practitioner sometimes did not see eye to eye, but Picken had a genius for resolving such difficulties and his patience was infinite. He worked for the harmony of the profession on both bodies, and was a wise counsellor. To him, more than to any other man, lies the credit of bringing about a proper understanding between the sections of the profession, and future generations of general and public health practitioners will reap the benefit of his work. Ralph Picken was a modest, unassuming man of great talents and tireless energy. He was a good companion and a staunch friend, and will be deeply mourned by all who knew him.

ARTHUR RUPERT HALLAM, M.D., F.R.C.P.

With the death of Rupert Hallam on August 29, at the age of 77, a further gap has been made in the ranks of the elder statesmen of British dermatology. He was a friend and admirer of those eminent dermatologists, Adamson, Barber, MacLeod, O'Donovan, and Roxburgh, who predeceased him within the past year, and, although not so well known as these giants of this century, he occupied a rightful place at the high table. He spent the whole of his active life in Sheffield and served the hospitals and university of that city with devotion and skill. In addition to being on the staff of the Royal Infirmary, Sheffield, which was his main appointment, he also gave dermatological service to the Sheffield Royal Hospital, the City General Hospital, Chesterfield Royal Hospital, and for a time, as a temporary measure, to Derbyshire Royal Infirmary.

Born in 1877, Rupert Hallam was the eldest son of Dr. Arthur Hallam, who, in addition to being in general practice, was one of the honorary surgeons to the Royal Infirmary, Sheffield, so that Rupert's association with the Infirmary started at a very early age. Educated in Germany and at the Sheffield Grammar School, he received his medical training in Edinburgh, graduating M.B., Ch.B. in 1901 and proceeding to M.D. in 1905. His original intention was to enter the family practice, but while he was holding various house appointments at the Royal Infirmary, Sheffield, the then dermatologist, Dr. Cocking, was taken ill and Hallam looked after the patients. His interest in dermatology having already been stimulated when a student in Edinburgh, he decided to make dermatology his life work. He was very conscious of the deficiencies in his knowledge and was arranging to work in Continental clinics, when, on the death of the dermatologist in 1911, he was appointed to the honorary staff of the Royal Infirmary. About this time the infant radiology was making its presence felt, and, since Rupert Hallam was the junior member of the staff, he was put in charge of the *x*-ray department. This fortuitous association stood him in good stead when the scope of radiotherapy in dermatology became fully realized, and he was in the fortunate position of having full control of his own superficial radiotherapy.

He served in the R.A.M.C. in the first world war, reaching the rank of major, and afterwards he started to build up his department.

As was customary at this time, he helped with the V.D. department, and as a result of his interest in venereology he was invited in 1921 to undertake an extensive world lecture tour on the social aspects of venereal disease. He often used to speak of this trip. Hallam was fully aware of the drawbacks of working in isolation, and took every opportunity to meet his colleagues both in this country and abroad. His holidays were usually spent visiting various clinics in Europe, and he often recalled with great pleasure the International Congresses held in Budapest and Copenhagen.

With the increasing amount of work in dermatology, and with the rapid growth of radiology, he gave up his *x*-ray diagnostic work in 1925 and about then started to establish a full-time dermatological unit in the Royal Infirmary. In this he was ahead of his time, and by 1930 a full-time clinical assistant was appointed to the department, a post which would now correspond to that of senior registrar. When the department was enlarged in 1949, it was unanimously agreed it should be called the Rupert Hallam Department of Dermatology as a tribute to his work. He felt strongly that the common diseases were the real problems and that rarities could be left to the stamp collectors. This attitude is borne out in his publications; he is probably known best for his papers on papular urticaria and chilblains, but he wrote on numerous other common dermatoses. Hallam always maintained that dermatology was essentially a branch of general medicine, and, when in 1936 he was considering the appointment of a second dermatologist, he himself submitted published work for election as a member of the Royal College of Physicians so that he could insist on the new appointee having the M.R.C.P. He was elected to the Fellowship of the College in 1940.

He had always hoped to retire before the age of 65, but on the outbreak of war his junior colleague was mobilized and Hallam was left to run a busy wartime clinic with inadequate assistance. His difficulties were increased by the complete destruction by enemy action of his consulting-rooms with all his records and library. He continued to work actively until 1944, when ill-health, caused by overwork, compelled him to retire. On retirement he went to live in the south-west and actively pursued his hobbies of painting, sailing, and gardening. His skill as an artist is shown by his self-

portrait which now hangs in the Royal Infirmary staff room, and of which a photographic copy is reproduced on the previous page.

Hallam was an original member of the British Association of Dermatology, being president in 1936, and was made an honorary member a few years ago. He also helped to found the North of England Dermatological Association in 1929 and was its president in 1930, and he became a member of the Section of Dermatology of the Royal Society of Medicine in 1923. A member of the B.M.A. for 49 years, he was a vice-president of the Section of Dermatology at the Annual Meeting at Eastbourne in 1931, vice-president of the Section of Dermatology and Venereal Diseases at the Annual Meeting in London in 1932, and president of the Section of Dermatology at the Bournemouth meeting in 1934.

Hallam was not an easy man to know; his tall, dignified, austere figure filled the casual acquaintance with awe, but those of us who knew and worked with him found him to be a most loyal and entertaining adviser and friend. His judgment and wise counsel were invaluable in solving the inevitable difficulties which arise from time to time in a hospital staff. As a teacher he was inspiring and gave the student every encouragement to learn dermatology. He will be greatly missed, particularly by those fortunate enough to have been his friends.—H. R. V.

E. F. F. writes: The first time I met Rupert Hallam was quite casual. As a first-year clinical student in the Faculty of Medicine of the University of Sheffield, I stepped aside to allow a tall, distinguished-looking, handsome, well-dressed man to pass me along a corridor of the Royal Infirmary. I was thanked in a kindly though, as some might regard it, a curt manner, and I realized that he was the new, and also the first, honorary radiologist appointed to the staff. This casual meeting was destined rapidly to develop into a friendship which, always becoming closer, lasted for more than fifty years.

This is not the place to record my feeling of great personal loss on Hallam's death, but to record something of what this quiet, unostentatious man did for the medical faculty of the university in the city of his birth, his colleagues on the staff, the students, and the community he served. He inaugurated and developed two important specialties; first, diagnostic radiology and later dermatology. He not only established these on a broad basis, but his unselfishness and lack of conceit were such that from amongst his own students he was always on the lookout for those who might follow him and maintain his ideals of work and service. That he succeeded is amply justified by the recognition awarded to those at present in charge of these two departments by their specialist colleagues, and is also testified by the annals of the Royal Society of Medicine.

It was fortunate for the wounded treated in Sheffield during the first world war that Hallam was in charge of diagnostic radiology, and his "staff sergeant" was Professor S. R. Milner, F.R.S., professor of physics at the university. They immediately devised so accurate a method for the location of foreign bodies in the tissues that it is now generally used. If the surgeon was unsuccessful in removing a metal fragment then he had only to blame himself or the inherent difficulties of the anatomical relationship.

It has been now recognized that the vested interests and prestige of two or more so-called "teaching hospitals" were the great obstacles to the smooth development of the medical faculties in some provincial universities. It was so in Sheffield, and it was overcome mainly by the foresight of Rupert Hallam. He began to experience the ill effects of continually working with *x* rays, and to lighten his commitments he took into partnership the newly appointed radiologist to the rival institution, who was a stranger to Sheffield. This partnership, owing to the integrity and loyalty of both, was a great success, and, although Hallam had been for some time the dermatologist to both institutions, it was this partnership which was the greatest factor in the blending of the two general hospitals into one co-ordinated whole.

Rupert Hallam was a delightful companion and colleague both on holiday and at work. He enjoyed the good things, interesting conversation, food, and wine. He had a keen zest for life, especially in the villages and country places, and his fingers were indeed "green." He had a great interest in his fellow men, literature, and history. He never lost interest in the work going on in his old department of dermatology, and was very proud that his successors had had the department named after him and a plaque erected commemorating the fact that he had inaugurated it. He was very artistic, and his pictures were accepted for various exhibitions. A short while ago, when on a visit to London, the authorities had allowed him to realize one of his ambitions, which was to make a sketch of Leicester Square. He told me that not one of the passers-by took the slightest interest in what he was doing; this neither surprised nor disappointed him. This latter episode epitomizes the character of the man. His control of his feelings was such that he rarely expressed surprise or astonishment; consequently this apparent aloofness was regarded by some as disdain, which was very far from the truth. The Medical Faculty of Sheffield owes much to Rupert Hallam.

MURIEL BARTON HALL, M.D.

Dr. Muriel Barton Hall died on September 5, aged 58. By her death the medical profession has lost an acknowledged leader in child psychiatry. Liverpool was the centre of her activities, but the influence of her character, her learning, and her wisdom extended far beyond.

Muriel Pickering-Jones graduated M.B., Ch.B. at Liverpool University in 1922, and in 1924 she married a fellow student, Dr. Stephen Barton Hall, who is director of the department of psychological medicine in Liverpool University. Thus began the close partnership which continued so happily and successfully up to the onset of her fatal illness. Mrs. Barton Hall's high intellectual qualities had been recognized during her student days, and soon after graduation she was appointed to the John W. Garrett International Fellowship in Bacteriology in the University of Liverpool. But her real interest was in clinical rather than laboratory subjects, and in children rather than adults—though her breadth of outlook dissuaded her from too early specialism. The experience which she gained in general medicine and paediatrics was the solid foundation upon which she began to build up her knowledge of psychiatry. In 1930 she proceeded to the degree of M.D. (Liverpool), and in 1931 she was appointed honorary psychiatrist to the Liverpool Child Guidance Clinic. During the eight years of her service to this clinic she became widely recognized as an accomplished child psychiatrist. In 1932 the Liverpool Psychiatric Clinic appointed her to the post of honorary psychiatrist, and in 1947 she was placed in charge of the psychiatric department at the Royal Liverpool Children's Hospital. It was a joy to see her at work with children and their parents, and to appreciate her acute powers of observation, her quick

and accurate appraisal of a situation, and her skill in giving advice. When necessary she could admonish without causing resentment; but in general it was her outstanding ability to explain, to persuade, and to inspire confidence that brought her success in the handling of these difficult cases. Psychiatry is perhaps heavier than any other branch of medicine in the demand it makes upon the intellectual integrity and personal character of its practitioners. Mrs. Barton Hall was self-critical without loss of self-confidence; her train of thought never seemed to be in danger of leaving the rails of common sense; her respect for human nature, with all its frailties, was always sincere, because sincerity was so deeply ingrained in her own constitution.

It was surprising that her physique could stand up to the many calls made upon her time and energy. Among the various offices which she held, always with distinction, were lecturer in child psychiatry in the University of Liverpool; consultant psychiatrist to Home Office approved schools; member of the Advisory Council on Child Care; and during the last war she was a member of the Standing Committee on Medical Women and War Services of the Medical Women's Federation, on the executive of which she served as a vice-president. At the time of her death she was chairman of the Liverpool Paediatric Club.

Mrs. Barton Hall wrote many papers for medical journals, both in this country and in North America. Her major work was her book *Psychiatric Examination of the School Child* (1947), which is widely considered to be an outstanding treatise on the subject.

There are many, both doctors and patients, who respected and appreciated her professional skill and were grateful for the help which she was always so ready to give; but those who, like her colleagues at the Royal Liverpool Children's Hospital, were within the circle of her personal friendship will be even more grateful for the memory of her wistful charm and her gentleness. Her example and influence will long be felt in the places where she did her life's work; and the dedication which she inscribed in her book may be quoted as a memorial to her own high qualities and her outlook on life: "To the young people whom it has been my privilege to examine and whose inherent goodness of character, loyalty to those who have hurt them most, and fine courage, often in face of intolerable hardship, have been a constant source of inspiration and encouragement."—N. B. C.

HOWARD K. GRAY, M.D., M.S., F.A.C.S.

Dr. Howard K. Gray, who had been on the surgical staff of the Mayo Clinic since 1932, died as a result of an accident on September 6.

Howard Kramer Gray was born at St. Louis on August 28, 1901. After graduating in science at Princeton University, he studied medicine at the University of Nebraska and at Harvard University, where he took the degree of M.D. in 1927. He was a Fellow in Surgery at the Mayo Foundation from 1928 to 1932, when he proceeded to the degree of M.S. (in surgery) of the University of Minnesota. In the same year he was appointed junior surgeon at the Mayo Clinic, becoming full surgeon and head of a section in general surgery in 1935. He was also professor of surgery at the Mayo Foundation Graduate School, University of Minnesota. During the second world war he served as a captain in the United States Naval Medical Corps, being awarded the Legion of Merit.

A member of many surgical societies, Dr. Gray had numerous friends in this country, and in 1951 he gave the Moynihan lecture at the Royal College of Surgeons of England, choosing for his subject "Clinical and Experimental Investigation of the Circulation of the Liver (with Practical Application to General Surgery)." With Walters and Priestley he was the author of *Carcinoma of the Stomach and Other Lesions*, published in 1942.

Dr. Gray married Lila Conrad in 1925, and he is survived by his widow and two children.

Sir HENEAGE OGILVIE writes: The accidental death on September 6 of Dr. Howard Gray of the Mayo Clinic removes a leading figure in American surgery, and a man greatly admired and widely loved in Britain. "Howdie" Gray was a general surgeon in every sense of the term. He was a first-class clinician, and a man whose judgment in difficult matters was almost infallible. In a centre that has for fifty years had a name for safe and successful surgery he was one of the best operators—safe, sure, gentle, ready to adapt his procedures to the problem in front of him. He was gentle and lovable, and had the great gift of inspiring trust and affection, of giving confidence to those who had come to him for operation and courage and cheerfulness in those who were recovering.

In two things he was pre-eminent in a country where good surgery is common. The first was his clinical or bedside wisdom, founded on a long memory of cases each of which had been to him a personal problem. His ward rounds were an education in methods of examination, in symptomatic treatment, in prognosis, and in the handling of humanity in trouble. His teaching in the theatre was equally imbued with the lessons of case experience. His second outstanding character was his ability as a teacher, as a writer, and above all as a speaker. Gray had mastered the lesson that few surgeons ever learn, that the lecture as delivered must be different from the lecture as written. The written lecture must be orderly, factual, and convincing. Its arguments must be consecutive, and it must contain all the facts upon which the arguments are based. It can be as dry and as heavy as the subject demands, for the man who reads it does so of his own volition and in his own time. The spoken lecture is delivered to an audience who have come in hope and who cannot afterwards get away. It must be simple and convincing, assertive rather than reasoned, and it must contain no tables, percentages, or any information that cannot be mastered in passing. Howdie Gray knew the exact approach to each audience. I heard him give three consecutive lectures: one to a small group of registrars and junior surgeons, one to the Section of Surgery at the Royal Society of Medicine, and one at the Royal College of Surgeons. Each was exactly right for the place, the audience, and the occasion.

Gray was a lovable man of many interests. At Princeton his reputation as a footballer was known throughout the States. Later he excelled at the less violent games, and loved to spend the day and to entertain his friends on his yacht on the Mississippi. He and his wife "Wint" had a delightful home in Rochester, where countless visiting British surgeons, particularly youngsters paying their first visit to the States, will remember their kindly hospitality, morning prayers at the breakfast table, and, in the evening, Howdie playing the organ.

The Services

Surgeon Rear-Admiral E. T. S. Rudd, C.B.E., R.N., has been appointed Honorary Surgeon to the Queen, in succession to Surgeon Captain A. H. Harkins, R.N.

Surgeon Rear-Admiral D. Duncan, O.B.E., R.N., and Surgeon Captain J. V. Williams, R.N., have been appointed Honorary Physicians to the Queen, in succession to Surgeon Rear-Admirals R. W. Mussen, C.B., C.B.E., and J. Hamilton, C.B., C.B.E., R.N., respectively.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **August 27** (No. 34) and corresponding week 1954.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	3	0	3	1	2	4	0	4	0	1
Dysentery	374	45	200	19	2	341	58	180	1	
Encephalitis, acute	7	1		0	2	1	0	0	0	
Enteric fever:										
Typhoid	11		2	1		1	0	0	1	
Paratyphoid	25		7	2		8	2	5(B)	0	
Food-poisoning	971	68		1		148	8		0	
Infective enteritis or diarrhoea under 2 years				43	73				7	15
Measles*	3,745	76	26	19	75	1,699	81	96	26	114
Meningococcal infection	13	0	15	0		16	2	4	2	
Ophthalmia neonatorum	34	3	6	0		38	0	7	0	
Pneumonia†	153	9	78	0		217	9	73	3	2
Poliomyelitis, acute:										
Paralytic	198	33	36	2	5	54	2	14	4	2
Non-paralytic	164	30				25	5			
Puerperal fever§	271	45	14	2		240	35	11	1	2
Scarlet fever	240	14	52	16	14	349	24	71	9	18
Tuberculosis:										
Respiratory	597	62	101	22		653	92	117	13	
Non-respiratory	80	7	18	4		90	5	23	2	
Whooping-cough	1,702	81	73	86	88	2,038	92	188	11	57

DEATHS in Great Towns	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	1	1		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	5	1	1	1	2	5	0	2	0	2
Influenza	2	0	0	0	0	3	1	0	0	0
Measles		0	0	0	1		0	0	0	0
Meningococcal infection		1	0				1	0		
Pneumonia	172	31	10	9	2	142	19	18	8	6
Poliomyelitis, acute	12	0			0	3	1			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	62	10	14	0	3	73	8	7	3	5
Non-respiratory		2	3	0	0		2	9	0	0
Whooping-cough	0	0	0	0	1	1	0	0	0	0
Deaths 0–1 year	170	26	22	5	17	193	18	25	8	16
Deaths (excluding stillbirths)	4,312	670	511	98	138	4,430	615	468	103	143
LIVE BIRTHS	7,172	1145	897	208	435	7,390	1046	425	214	404
STILLBIRTHS	170	25	19			163	21	26		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Poliomyelitis

During the week ended September 3 (35th week) 398 cases of acute poliomyelitis were notified in England and Wales, a disappointing increase of 36 on the previous week's total of 362. The proportion of non-paralytic cases (192) to paralytic cases (206) was, however, higher than in the previous week, when the corresponding figures were 164 non-paralytic and 198 paralytic. Notifications for the 35th week of 1955 are higher than in any corresponding week since 1950 (when the figure was 491), but the percentage of paralytic cases (51.8%) is smaller than in the corresponding weeks of 1954 (62.0%), 1953 (54.9%), 1952 (70.0%), and 1950 (61.5%). In the 35th week of 1951 only was the percentage of paralytic cases lower (39.3% of a total of 89 cases). Deaths from acute poliomyelitis in the great towns numbered 6 (12 in the previous week).

The East and West Ridings of Yorkshire had the highest regional notification rate in the 35th week, followed by Greater London. The lowest rate was in the northern region. On a county basis Middlesex, London, West Riding of Yorkshire, and Derby headed the list, followed by Essex, Kent, and Gloucester. In the County of London in 1955 to date the incidence of poliomyelitis has reached abnormally high proportions with an incidence of uncorrected notifications of 15.2 per 100,000. The following boroughs, etc., in England and Wales have had particularly high rates in the year to date (figures are for cases notified by September 3, with rate per 100,000 of the population in parentheses): Barnsley C.B. 71 (94.9), Hoyland Nether U.D. 11 (69.4), Willesden M.B. 104 (58.7), Wombwell U.D. 11 (58.6), Dover M.B. 19 (55.8), Stepney Met. B. 48 (49.0), Poplar Met. B. 31 (43.2), Marshland R.D. 7 (42.8), Thurrock U.D. 41 (42.3), Worsborough U.D. 6 (41.8), Wisbech M.B. 6 (34.9), Southwark M.B. 33 (34.6), Rushden U.D. 5 (30.2), Lewisham M.B. 63 (28.1), and Aylesbury R.D. 8 (25.3). For England and Wales as a whole the rate for the year so far is approximately 6.7 per 100,000.

The Ministry of Health states that, while it is hoped that the seasonal fall will commence in the next week or two, the possibility cannot be entirely excluded of further rises to a late peak as in 1949.

In Scotland 53 cases of poliomyelitis were notified during the week ended September 3; 23 of these were in Glasgow.

Week Ending September 3

The notifications of infectious diseases in England and Wales during the week included: acute poliomyelitis 398, scarlet fever 228, whooping-cough 1,511, diphtheria 6, measles 2,618, acute pneumonia 179, dysentery 400, paratyphoid fever 34, and typhoid fever 10.

Infectious Diseases

The largest fluctuations in the number of notifications of infectious diseases in England and Wales during the week ending August 27 were a fall of 1,822 for measles, from 5,567 to 3,745, and increases of 583 for food-poisoning, from 388 to 971, and 90 for dysentery, from 284 to 374.

The largest declines in the notifications of measles were 140 in Southampton, from 276 to 136, 121 in Devonshire, from 251 to 130, 106 in Glamorganshire, from 422 to 316, 101 in Buckinghamshire, from 167 to 66, 81 in Gloucestershire, from 153 to 72, 80 in Sussex, from 299 to 219. 240 cases of scarlet fever, 6 more than in the preceding week, were notified, and there was no change in the local trends. 1,702 cases of whooping-cough were notified, 18 more than in the preceding week. The largest variations in the returns of whooping-cough were a rise of 53 in Durham, from 117 to 170, and a fall of 34 in Warwickshire, from 130 to 96. 3 cases of diphtheria were notified, the same number as in the preceding week.

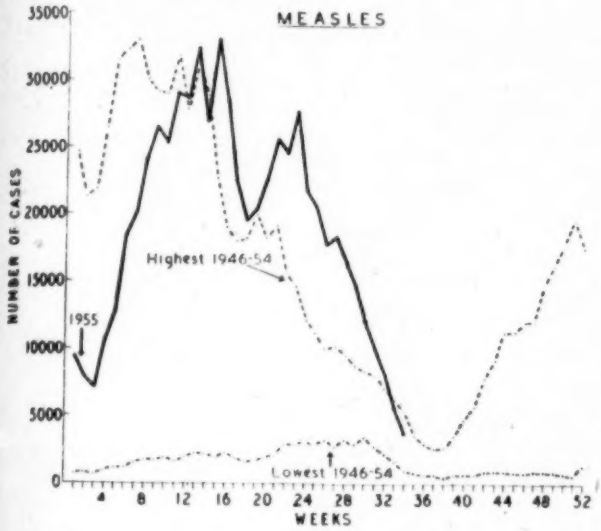
The largest number of notifications of paratyphoid fever was in Worthing R.D., Sussex, where there were 6 cases. There was an outbreak of food-poisoning in Bolton C.B., 361 cases being notified.

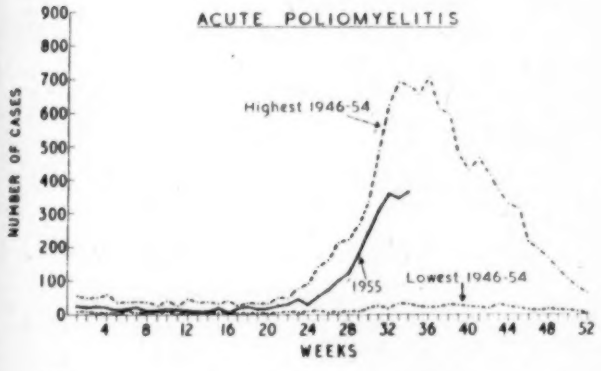
The rise in the number of notifications of dysentery was mainly contributed by Lancashire, where the cases rose from 59 to 119. The largest returns were Lancashire 119 (Liverpool C.B. 39, Bolton C.B. 15, Darwen M.B. 14), London 45 (Southwark 10), Yorkshire West Riding 34 (Leeds C.B. 19), Warwickshire 20 (Birmingham C.B. 10), and Durham 18 (South Shields C.B. 9).

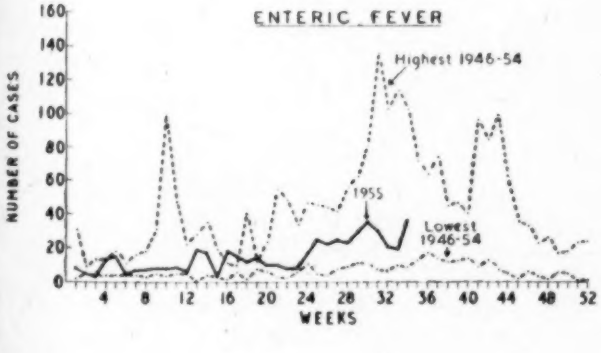
In Scotland the largest returns of dysentery were Glasgow 117, Edinburgh 24, Dundee 17, Ayr county 12, and Greenock 10.

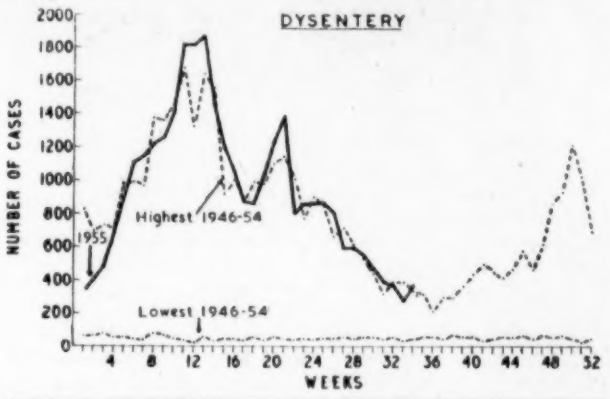
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1946–54 are shown thus ------, the figures for 1955 thus ———. Except for the curves showing notifications in 1955, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Medical News

Symposium Neuroradiologicum.—The fourth Symposium Neuroradiologicum was held in the Senate House of the University of London from September 12 to 17. This, the first specialist branch of radiology to hold regular international meetings, was inaugurated in 1939 at Antwerp, when a few physicians interested in the radiology of the skull came together to discuss common problems. In his opening address to the fourth symposium, the president, Dr. JAMES BULL, reminded those attending that this was a symposium, not a congress. Its purpose was the free exchange of ideas, with discussion at as informal a level as possible. It was only after the symposium had been planned that it was discovered that the Second International Congress of Neuropathology was meeting in London in the same week, and the opportunity of arranging a joint session was too good to miss. This had accordingly been arranged on the subject of tentorial herniation. Altogether some 70 papers had been arranged for the symposium, embracing such subjects as cerebral pneumography, tumour diagnosis, angiography, stereotaxy, and isotopes in neuroradiological diagnosis. Among the countries represented in their authorship were Canada, Denmark, the United States, France, Hungary, Sweden, Portugal, Italy, Belgium, Algeria, Germany, Holland, and Norway. In addition a technical exhibition was held in connexion with the symposium.

Medical Libraries.—Representatives of medical libraries from fifteen countries met in Brussels on September 10 to continue discussions begun at the First International Congress on Medical Librarianship held in London two years ago (see *Journal*, 1953, **2**, 274). The meeting formed part of the International Congress of Libraries and Documentation held under the auspices of the Belgian Government. Professor P. LAMBIN, of the Faculty of Medicine at Louvain, presided. Mr. W. R. LE FANU (Royal College of Surgeons of England), chairman of the Congress Committee in 1953, gave a progress report on the steps taken towards establishing an international body since 1953. It was agreed unanimously that an International Association of Medical Libraries and Documentation Centres should be formed, with membership open to both institutions and personnel. A committee was elected and entrusted with the drafting of a constitution. Proposals by Mr. F. N. L. POYNTER (Wellcome Historical Medical Library) for establishing national centres for the exchange of duplicate medical periodicals and books between libraries were also accepted unanimously, and Unesco promised financial aid. Among other subjects discussed was the need to instruct medical students in the proper use of the medical library, and a formal resolution urged that this should form part of the curriculum in every medical school. The relations between the library and the medical profession also provoked lively discussion, and Professor E. R. CUNNINGHAM (U.S.A.) suggested that the growing complexities of medical literature and its documentation

called for the establishment of a special literature section in every professional association. She said that the American Medical Association had already agreed to this, and that the new section would have its first meeting at next year's annual convention.

Chartered Society of Physiotherapy: Diamond Jubilee.—To mark its 60th anniversary the Chartered Society of Physiotherapy entertained the Press on September 7. Sir HAROLD BOLDERO, Chairman of the Council, who presided, spoke of the society's growth. In 1895, he said, a group of four women, including Dame Rosalind Paget and Miss Lucy Robinson, formed the society and named it the Society of Trainee Masseuses. Thereby a new profession was founded at a time when women were having a hard struggle to enter the older established professions. The aims of the society were to provide facilities for adequate training in massage, and, second, to ensure a code of ethics for those who practised after qualification. At the society's first meeting "Rules for Masseuses" were drafted, including "No massage to be undertaken except under medical direction." To-day the society, renamed the Chartered Society of Physiotherapy in 1942, was not only a training and examining body, but also the professional association of chartered physiotherapists. There were 15,000 names on the society's register, and Sir Harold hoped that State registration would come within the life of this Parliament. The Diamond Jubilee Congress will be held in London from September 22 to 24, and will be opened by the Minister of Health. The Earl and Countess of Mountbatten will be the principal guests at the society's dinner on September 22.

Health of Seafarers.—The joint International Labour Office and World Health Organization committee on the hygiene of seafarers has recently issued its second report (*Wld Hlth Org. techn. Rep. Ser.*, 1955, No. 92, price 1s. 9d.). The report discusses medical advice by radio, the examination of seafarers for tuberculosis, medicine chests and their contents, and venereal disease. Among the British members of the committee was Professor W. M. FRAZER, emeritus professor of public health, Liverpool University, and, as an adviser, Dr. E. L. CALDWELL-SMITH, chief medical officer of the British Shipping Federation. The chapter on medicine chests for ships without doctors includes a suggested minimal list of medicaments, surgical instruments, and appliances. The committee recommends that this section of its report should be submitted to governments for their guidance in instituting or revising their regulations on medicine chests.

Another Medical Visit to Russia.—Fourteen British doctors and a lay member of a regional hospital board left England on September 8 for a three-week visit to Russia, at the invitation of the Soviet Ministry of Health. Their main object is to study the practice of preventive medicine. The party consists of the following:

Dr. D. B. BRADSHAW (Department of Preventive Medicine and Public Health, Leeds), Professor C. FRASER BROCKINGTON (Department of Social and Preventive Medicine, Manchester), Dr. L. J. H. BURTON (Central Council for Health Education), Dr. H. B. O. CARDEW (Medical Practitioners' Union), Dr. B. R. CLARKE (Northern Ireland Tuberculosis Authority), Dr. J. J. R. DUTHIE (Department of Medicine, Edinburgh), Dr. S. GOTTLIEB (Hon. Sec., Socialist Medical Association), Dr. J. D. KERSHAW (M.O.H., Colchester), Dr. S. LEFF (M.O.H., Willesden), Dr. BARBARA MCPHERSON (Prophit scholar, Royal College of Physicians), Dr. M. S. MILLER (practitioner, Glasgow), Mr. R. SARGOOD (S.W. Metropolitan Regional Hospital Board), Dr. R. S. SAXTON (practitioner, Brighton), Dr. A. G. M. SEVERN (M.O.H., Pontypridd), and Dr. ALICE STEWART (Social Medicine Unit, Oxford).

Sir Harry Platt, P.R.C.S., will visit Canada and the United States during October as the guest of the Royal College of Physicians and Surgeons of Canada at their annual meeting in Quebec, and of the American College of Surgeons during the clinical congress in Chicago, where he will take part in the postgraduate course. He will also deliver the F. H. Albee memorial lecture at the Kessler Institute, West Orange, New Jersey, and a Balfour lecture at Toronto University.

Dr. H. Stanley Banks, who has recently retired from his post as senior physician at the Park Hospital, London, is joining the headquarters staff of the Medical Research Council as medical officer (part-time) in charge of publications.

COMING EVENTS

Medical Defence Union.—Annual general meeting, September 20, 3.15 p.m., at the Large Physics Lecture Theatre, the Fort, Bristol University. All professional members in benefit entitled to attend and vote.

National Smoke Abatement Society.—Annual conference at Bournemouth, September 28–30. The Government's Clean Air Bill will be the principal subject for discussion.

European Association Against Poliomyelitis.—The third symposium will be held at Zurich, under the presidency of Professor G. FANCONI, on September 29 and 30. Inquiries to Dr. P. RECHT, 67, Boulevard Auguste Reyers, Brussels.

NEW ISSUES

Journal of Neurology, Neurosurgery, and Psychiatry.—The new issue (Vol. 18, No. 3) is now available. The contents include:

TUBERCULOUS MENINGITIS OF ACUTE ONSET. K. B. Taylor, H. V. Smith, and R. L. Vollum.
THE PATHOLOGICAL EFFECTS PRODUCED BY SERA OF ANIMALS IMMUNIZED WITH FOREIGN NERVOUS OR SPLENIC TISSUE. PART I: INTRACISTERNAL INJECTION OF SERUM. E. Weston Hurst.
SPINO-CORTICAL FIBRES IN MAN. P. W. Nathan and Marion C. Smith.
ON THE MUSCULAR RIGIDITY AND HYPERREFLEXIA DUE TO HYPOTHERMIA IN MAN, WITH OBSERVATIONS ON THE ACCOMMODATION OF PERIPHERAL NERVE. John A. Simpson.
CONGENITAL HEREDITARY VERTICAL NYSTAGMUS. W. I. Forsythe.
A BENIGN "TUMOUR" OF THE CEREBELLUM. D. R. Oppenheimer.
DYSPHASIA FOLLOWING RIGHT TEMPORAL LOBECTOMY IN A RIGHT-HANDED MAN. G. Ettlinger, C. V. Jackson, and O. L. Zangwill.
IMPAIRED IDENTIFICATION OF FACES AND PLACES WITH AGNOSIA FOR COLOURS. C. A. Pallis.
RAUWOLFIA SERPENTINA (SERPASIL) IN PSYCHIATRY. J. D. Glynn.

Issued quarterly: annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Tuesday, September 20

LIBRARY ASSOCIATION (MEDICAL SECTION).—At Chancer House, Malet Place, W.C.1, 7 p.m., Lieutenant-Colonel F. B. Rogers: Seven Problems of Medical Index Publishing.
ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Mr. A. Dickson Wright: Sciatica of the Arm.

Wednesday, September 21

HYPNOTHERAPY GROUP.—At Royal Society of Medicine, 8 p.m., Dr. N. S. Sherrard: Mind is the Only Thing That Matters.

Saturday, September 24

NORTH-EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY.—At Black Notley Hospital, near Braintree, Essex, 11 for 11.15 a.m., joint meeting with East Anglian Society for the Study of Tuberculosis and Diseases of the Chest. 11.30 a.m., Mr. R. W. Reid: Treatment of Renal Tuberculosis; 2 p.m., Dr. C. J. Stewart: Recent Experience of Tuberculosis Control in Scandinavia; 2.40 p.m., Mr. M. C. Wilkinson: Synovectomy and Débridement in Skeletal Tuberculosis.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Hales.—On August 25, 1955, at Freedom Fields Hospital, Plymouth, to Mary (formerly Notley), wife of John Hales, M.B., B.S., of Ridgeway House, Plympton, Devon, a brother for Kathryn.

DEATHS

Davies.—On August 11, 1955, at his home, Glasfryn, Bala, Merioneth, Arthur Lewis Davies, M.R.C.S., L.R.C.P., J.P., aged 70.
Ferguson.—On August 8, 1955, at Beaconsfield, 12, Princes Avenue, Walsall, Staffs, Donald John Ferguson, M.B., Ch.B.
Gillespie.—On August 21, 1955, at Madison, Wisconsin, U.S.A., Noel Alexander Gillespie, D.M., F.F.A.R.C.S., aged 50.
Hall.—On August 21, 1955, George Hall, M.D., late of Church Road Cottage, West Lavington, near Midhurst, Sussex.
Holme.—On August 18, 1955, at 47, Brassey Avenue, Hampden Park, Eastbourne, Sussex, Crampton Whitaker Holme, M.B., C.M., aged 84.
Leeman.—On August 23, 1955, at 10, South Avenue, Littleover, Derby, Percival Garmany Leeman, *M.C.*, M.B., B.Ch., aged 69.
Meller.—On August 25, 1955, Emily Matilda Meller, M.B., B.Ch., of Cowbridge, Glam.
Moriarty.—On August 25, 1955, at 20, Purcell's Avenue, Edgware, Middlesex, Gerald Irving Moriarty, M.D., aged 76.
Thomson.—On August 21, 1955, at a nursing-home, Dundee, Emily Charlotte Thomson, M.B., C.M., late of Bonnyton House, near Arbroath, Angus, aged 91.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Homesickness

Q.—*What is the psychological significance of homesickness? If prolonged for more than a short time, what ill effects is it likely to have? When is treatment indicated, and what should it be?*

A.—Homesickness indicates an over-dependence on the home surroundings and particularly upon the mother. Adolescents are usually the victims, but it is common in children. The developing child must leave behind the continued security of home if he is to attain independence. Parents accept this—in theory—but often cling to their children in unexpected ways. Thus the parental attitude is frequently at the base of the trouble. A nostalgic yearning for the idealized home may appear when the boy or girl faces the difficulties of school. If the homesickness is episodic—that is, occurs for the odd half an hour—no treatment is necessary. Homesickness which lasts for weeks and interferes with work may point to a depressive element in the personality, and schizophrenic symptoms may manifest themselves by prolonged bouts of homesickness.

An assessment of the state of mind should always be made when homesickness is prolonged, as a decision about treatment depends on this. Simple measures should be tried first—for example, a small dose of amphetamine in the morning—and, if sleep is disturbed by nightmares or sleep-walking, a mild sedative may be given at night for two or three weeks. Adolescents are wonderfully resilient, and in the vast majority the condition does not call for special investigation.

Treatment and Prognosis in Sarcoidosis

Q.—*What recent advances have there been in the treatment of sarcoidosis? What is the prognosis in this condition?*

A.—It cannot be claimed that any considerable advances have recently been made in the treatment of sarcoidosis. The long-term administration of anti-tuberculosis drugs has been tried, with some suggestion of benefit,[1] though this has not been established in a statistically satisfactory way. Cortisone or corticotrophin causes regression of those lesions of sarcoidosis which are in a reversible stage, but unfortunately in many cases these lesions return when the hormone is discontinued, no matter how gradually it is withdrawn. The behaviour of sarcoidosis treated with these hormones could well be explained on the hypothesis that they cause a temporary remission in the reversible lesions, and that what happens when the hormone is withdrawn depends upon what would have been the natural course of the condition. If it would in any case have cleared, a permanently satisfactory result may appear to have been obtained by the hormone; if it would have remained stationary, withdrawal of the hormone will be followed by return to the original state; if its natural course was towards deterioration, withdrawal will be followed by what appears to be a severe "flare-up" of the condition. Nevertheless, where the lesions are so placed that the active phase may result in serious destruction of function, the use of the hormones is fully justified—for example, for the ocular manifestations. On the other hand, experience has suggested that the hormones are very unsatisfactory in the treatment of the skin lesions. So far as the lung lesions are concerned, there is a possible place for the hormones in the symptomatic treatment of the advanced case with irreversible lung changes. In these cases the dyspnoea may be relieved by quite moderate doses of cortisone. It should be realized, however, that this treatment is essentially symptomatic, and that no effect on the irreversible fibrotic changes in the lungs can be expected. On the whole, the results obtained with cortisone and corticotrophin for sarcoidosis must be regarded as disappointing.

With regard to prognosis, a considerable proportion of cases of sarcoidosis regress spontaneously. So far as the lung changes are concerned, when such spontaneous regression occurs the outlook is excellent, since they very rarely, if ever, recur. When irreversible fibrosis has occurred the prognosis is similar to that of pulmonary fibrosis due to other causes; while some cases remain stationary with moderate disability almost indefinitely, others become liable to intercurrent secondary infection and eventually succumb from pulmonary insufficiency, sometimes complicated by right ventricular failure. Only very few cases develop frank tuberculosis. If this occurs, lesions which have remained in a distinctively sarcoid phase may resolve spontaneously, and the condition then becomes susceptible to antibacterial drugs, which may therefore cause considerable improvement.

REFERENCE

[1] Hoyle, C., Dawson, J., and Mather, G., *Lancet*, 1955, **1**, 638.

Sweet Toothpastes and Caries

Q.—*It is common knowledge that most toothpastes are loaded with sugar. The present vogue is to believe that dental decay is largely due to the fermentation of sugar left in the mouth after ingestion of sugar-containing foods. If correct, how do these statements match? Would one lose anything by using a simple toilet soap in place of toothpaste?*

A.—The leading brands of proprietary toothpastes at present on the market do not in fact contain any sugar at all. The apparently sweet taste is due to the glycerin incorporated in many pastes, and where extra sweetening is required for flavour saccharin is added. Particles of toothpaste left between the teeth after brushing are therefore unlikely to damage the teeth.

There is no danger or disadvantage in using toilet soap in place of toothpastes, except that the taste is not so pleasant.

Peptic Ulcer at Sea: Haemorrhage and Perforation

Q.—*How should a ship's doctor, with little or no practice in major operations, when far from port and without skilled help, treat serious haemorrhage from, or perforation of, a peptic ulcer?*

A.—In a case like this the bleeding is presumed to be the first serious haemorrhage the patient has had, for a person with recurrent bleeding from a peptic ulcer ought not to be taking the risk of travelling under such conditions. The haemorrhage may therefore be expected to cease spontaneously provided the patient is kept quiet and the gastric juice is given something to digest. He should not leave his bed, and an injection of morphine, gr. ¼ (16 mg.), should be given in order to provide mental as well as physical rest. Small quantities (3 to 4 oz.—about 100 ml.) of milk, "Horlicks" or "Benger's Food," or egg and milk should be given every two hours, and patent baby cereal or fine porridge, and plain biscuits with butter may soon be added. Milk puddings, scrambled egg, and pounded fish and chicken are given as appetite returns, and an antacid powder should follow each feed, the dose varying with the amount of food being taken. Replacement of blood must depend on the amount lost; whereas blood transfusion may be ideal, under the special circumstances the administration of iron will probably suffice until port is reached and the patient can be sent to hospital.

Perforation of a peptic ulcer should be treated by emptying the stomach with a Ryle's tube, which should then be connected to a simple three-bottle hydraulic suction apparatus—Wangensteen suction—to keep the stomach empty. Morphine should be given in appropriate dosage every four hours; for the ordinary adult gr. ¼ (10 mg.) at each dose. Fluid should be administered by rectal drip, in

the form of plain water or 1/5 normal saline solution, up to 3 litres being thus given in 24 hours. The intravenous route is to be employed only when rectal fluid is not tolerated. After three days of this regime small quantities of fluid food may be given by the mouth as the first step towards introducing the sort of diet described above, and the morphine should be stopped.

Pipetting of Volatile Solvents

Q.—*Apart from the risk of getting a mouthful, is there any serious hazard in the frequent pipetting (30 times a day) of volatile substances such as chloroform? A research chemist has to do this in chromatography, and is anxious about it. Are any special precautions indicated?*

A.—The solvents used in chromatography vary so widely in their toxicity that it is difficult to lay down any specific safety rules for such procedures. Those procedures involving the use of volatile solvents "running" on paper, etc., demand the use of well-ventilated rooms or exhaust ventilation and fume cupboards. The technique is widely used, and, as it is being developed continuously, new materials, some of comparatively unknown biological activity, are constantly being introduced.

The hazards of chromatography are certainly not confined to pipetting but are more likely to be met in the general handling of the solvents and exposure to their vapour, especially during "runs" on paper. Chemists are sometimes surprisingly unaware of the toxic properties of substances they handle, and, like doctors in touch with infectious disease, they often but not always "get away with it." Good reference books such as Dr. Ethel Browning's *Toxicity of Industrial Organic Solvents* (H.M.S.O., 1952) should be available, and manufacturers are usually able to supply advice on the toxic hazards associated with the use of their products.

Safety pipettes, which avoid the need for sucking by mouth, are available for use with very poisonous or otherwise dangerous liquids—for example, acids. There is no reason why they should not be used for chloroform, though it is doubtful if their use would reduce the risk from handling chloroform in unsatisfactory environmental conditions.

Curved Penis and Sexual Capacity

Q.—*A young man intending marriage has sought advice because his erect penis curves slightly to the left, so that the tip is offset by about 2 in. (5 cm.) from the median plane. The flaccid organ appears normal. What are the causes of this? Is penile curvature of this degree liable to interfere with satisfactory intercourse, and what steps, if necessary, should be taken to correct it?*

A.—I suspect that actually the penis in question is quite normal, for I have often listened to young unmarried and inexperienced men describing the alarming peculiarities they have noticed in themselves, and have afterwards found nothing wrong with them at all. A small degree of curvature is normal. A pathological curvature would be due to fibrous cavernositis, and this is exceedingly rare in the young. But let us suppose that it actually exists in this case. He can still be assured that it will not prevent coitus or get worse, or interfere with micturition. If this young man has any difficulties in coitus on marrying, it will be because he has developed a sexual neurosis and fears that he may find himself impotent. Emphatic reassurance is what he needs most.

Vitamin A and Ichthyosis

Q.—*Is vitamin A of value in the treatment of ichthyosis? If so, in what dosage and for how long should it be administered, and should any variation in dosage be made for age?*

A.—There is clearly an important relationship between vitamin A and keratinization. Clinical experience shows that a small proportion of patients with ichthyosis benefit from the administration of vitamin A whether or not there is a low serum level of vitamin A. Questions of absorption and utilization may enter into the problem, but there are many other factors involved in ichthyosis, including the genetic, hormonal, and climatic. Doses of 100,000 to 250,000 i.u. daily may be given for two to three months, depending on the age of the patient, to determine empirically whether it is of value in a particular case. If helpful, then courses of treatment governed by the response should be given. Toxic effects on the liver are recorded, but are rare with this dosage.

A Good Head of Hair and Cancer

Q.—*During the past four years whilst engaged in general practice I have seen about 15 men die of cancer, mostly of the stomach, bronchus, or prostate. All were over 50 years of age, and I noticed that all had a good head of hair. Is there a recognized relationship between growth of hair and the liability to cancer, or are my observations just due to coincidence?*

A.—There are no records of this association in easily available cancer literature, but it would be unwise to dismiss your observations as coincidental.

Dangers of Selenium in Dandruff Shampoo

Q.—*Selenium sulphide is contained in a shampoo for dandruff ("selsun"). The makers give most careful instructions about thorough rinsing after use and cleansing of the hands. What are the dangers if these instructions are neglected?*

A.—Selenium sulphide is known to have a chemical action on keratin and may therefore damage the horny tissues of the skin and nails if it is used indiscriminately. This, no doubt, is the reason why the makers recommend careful cleansing of the hands after the use of "selsun." It should not be assumed from these instructions that the proper use of selsun carries any notable risk. The writer has known patients use selsun with gross neglect of the makers' instructions without any harm resulting. If the material is used as instructed there is a wide margin of safety.

NOTES AND COMMENTS

Corrections.—It is regretted that one of the formulae in the answer to the question on significance and the standard deviation ("Any Questions?" September 10, p. 692) was printed incorrectly. The standard deviation of the difference between two randomly selected observations from the same population should have been given as $\sqrt{2}\sigma$, not $\sqrt{2\sigma}$.

We much regret that Professor F. A. E. Crew's name was wrongly spelt in the heading to the review of the *Medical History of the Second World War—Army Medical Services* (Administration, Vol. II) published in our issue of September 3 (p. 605).

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